A stochastic model featuring acid induced gaps during tumor progression

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Abstract

In this paper we propose a phenomenological model for the formation of an interstitial gap between the tumor and the stroma. The gap is mainly filled with acid produced by the progressing edge of the tumor front. Our setting extends existing models for acid-induced tumor invasion models to incorporate several features of local invasion like formation of gaps, spikes, buds, islands, and cavities. These behaviors are obtained mainly due to the random dynamics at the intracellular level, the go-or-grow-or-recede dynamics on the population scale, together with the nonlinear coupling between the microscopic (intracellular) and macroscopic (population) levels. The wellposedness of the model is proved using the semigroup technique and 1D and 2D numerical simulations are performed to illustrate model predictions and draw conclusions based on the observed behavior.

1 Introduction

Irrespective of the sufficiency or deficiency of oxygen supply, cancer cells exhibit excess use of glycolysis [43, 46]; this is the so-called Warburg effect. The reason may be: (i) reduction in the number of mitochondrian after successive replication [46], (ii) evolutionary selection of glycolytic phenotype under hypoxic and stressful conditions prevalent in tumor [31]. These combined with the enhancement of acid extruders, like MCT, NHE, NDBCE, H^+-ATPase, result in excretion of the acidic metabolic byproducts on the extracellular region [43]. Furthermore, the tumor local environment being poorly and erratically vasculated results in reduced dissipation of interstitial acid [47, 43]. Altogether, the cancer local environment becomes relatively acidic compared to the normal physiological levels. As a consequence, there is a twofold boon for cancer cells: (i) the relatively alkaline intracellular pH (pH_i) [43, 48] promotes cell proliferation, evasion of apoptosis, cytoskeleton remodeling, etc. due to rapid acid extrusion [48, 16, 27], and (ii) the relatively acidic extracellular pH (pH_e) results in degradation of ECM fibers, p53 induced apoptosis of stromal cells, metastatic dissemination [48, 36, 22]. The acidic pericellular pH also results in accumulation of *cathepsin B* near the cell membrane and the subsequent release of active *cathepsin B* on the extracellular side [38]. This in turn stimulates the production of proteolytic enzymes. Because of evolutionay selection of stable invasive phenotypes [52], cancer cells themselves are not negatively affected by acidic pH_e. To summarize, the reverse pH gradient plays a significant role in contributing to the malignancy of the cancer. The latter can be qualitatively categorized based on its strength of invasion which in turn can be judged based on the histological patterns generated by a progressing tumor. Infiltrative growth pattern (INF) classification is one such classification scheme, as defined by the *Japanese Gastric Cancer Association* [1, 20]. Based on this, invasion can be assigned to three categories:

1. INFa : An expanding tumor core with a clear separation between its boundary and the stromal cells.
2. INFb : An intermediate stage of tumor expansion with or without clear separation from the stromal cells.

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3. INFc : An expanding tumor core whose boundary cells have infiltrated the stromal cells and there is mixing of tumor and stromal cells.

The INFa stage marks the appearance of a gap between cancer cells and stromal cells. This gap may be composed of the cellular byproducts secreted mostly by the cells on the progressing boundary of the tumor core. This progression can be either due to cell proliferation or due to spatial movement induced by random motion or taxis [39, 12]. In either case the cells rely on glycolysis for energy production [46, 44, 3], as a result of which the gap consists of acidic metabolites. The acidic contents enhances in turn cell motility [36] by making room for movement through degradation of ECM fibres [38, 15] and inducing apoptosis in normal cells [22].

To our knowledge the first account on an acidity-induced gap was given in [14], where a reaction-diffusion model with solution-dependent diffusion coefficient was proposed and approximate travelling wave solutions were obtained under appropriate conditions. The existence of the gap (in the case of human squamous cell carcinomas of head and neck) was histologically verified with the success rate of 14/21. More recently a slightly modified version of the model in [14] was proposed in [30] and using asymptotic analysis the parameter space was classified for different invasive behaviors of cancer cells mediated by extracellular acid. Thereby, the dependency of the gap on the model parameters was established, finding that gaps occur in mildly aggressive cancer cells (i.e., cancer cells having competition strength and acid induced mortality rate similar to that of normal cells). On the contrary, in [14] the parameter dependency for the gap suggested its presence only in the case of aggressive cancer cells (i.e. cancer cells inducing high mortatility rate for normal cells via extracellular acidity). This contrast and a thin 67% success rate of the experimentally observed gap in [14] may suggest that its appearance is not a common phenomenon of cancer invasion and may vary from one type of cancer to the other. Moreover, the differences in the model equations point out that additional nonlinearities and cellular uncertainties may provide dynamics rich enough to generate acid induced infiltrative patterns.

Motivated by these observations we rely on the *go-or-grow* hypothesis (see [11, 13]) to propose a highly nonlinear stochastic model for the gap formation between cancer and stromal cells. Here we use acidity as the key ingredient regulating the appearance and disappearance of a gap. Also the nonlinear coupling between the proton dynamics and cell-population dynamics leads to interesting infiltrative patterns of tumor cells. The model builds on the one we proposed in [19] and extends a deterministic setting proposed in [41] to describe the interdependent behavior of normal tissue and tumor under the effect of intra- and extracellular proton evolution: the present model includes most of the features therein and moreover accounts for cross diffusion between cancer cells and extracellular protons and for randomness in the intracellular proton dynamics. In Section 2 we setup the model then prove in Sections 3 and 4 its wellposedness by using the semigroup theory, which is convenient for the analysis in L^p spaces. Moreover, the mild-form representation of solutions enables us to handle general a.s. continuous Gaussian processes. Numerical simulations are performed in Section 5 in order to verify the model predictions and to get a glimpse of different infiltrative patterns of cancer cells induced by acid dynamics. We conclude this work in Section 6 with a short discussion of the main findings. The Appendix contains definitions of the employed function spaces, properties of operators, and some results needed in the proofs.

2 Modeling

In this section we present the equations describing the biological phenomenon of interest and justify the terms involved. The involved variables H_i, H_e, C, and N have the following meaning:

- C denotes the population density of cancer cells; it is measured in $cells/vol$.
- N is the population density of stromal (normal) cells; it is measured in $cells/vol$, too.
- H_i represents the concentration of protons in the intracellular region of a cancer cell; it is measured in Mol/vol.
- H_e is the concentration of protons in the extracellular region due to cancer cells; it is measured in Mol/vol, too.

The system of equations describing the dynamics of the proton concentrations and cell population densities writes:

$$\frac{d}{dt}H_i = J(C/K_C)[-T_1 - T_2 + T_3 - Q + q_1] + \gamma_\xi J(C/K_C)\frac{H_i}{K_w}\xi_t \tag{1a}$$

$$\begin{aligned}\frac{\partial}{\partial t}H_e &= J(C/K_C)[T_1 + T_2 - T_3] - q_2 H_e + \gamma_D \Delta H_e + \nabla\cdot\Big(\gamma_g g(\frac{H_i}{K_w}, \frac{H_e}{K_w}, \frac{C}{K_C})\nabla C\Big) \\ &\quad + \nabla\cdot\Big(\gamma_h h(\frac{H_e}{K_w}, \frac{N}{K_C})\nabla N\Big)\end{aligned} \tag{1b}$$

$$\begin{aligned}\frac{\partial}{\partial t}C &= C(1-\frac{C}{K_C})(\Lambda_1(\overline{H}_i, \overline{H}_e) + \Lambda_2(\overline{H}_i, \overline{H}_e)) + \nabla\cdot\Big(\gamma_a a(\overline{H}_i, \overline{H}_e, \overline{C}, \overline{N})\nabla C\Big) \\ &\quad - \frac{\gamma_b}{K_w} b(\overline{H}_i, \overline{H}_e)\nabla H_e \cdot \nabla C\end{aligned} \tag{1c}$$

$$\frac{d}{dt}N = -\gamma_N \frac{C}{K_C}N + \Big(-\gamma_{\Lambda_3}\Lambda_3(\overline{H}_e) + \gamma_{\Lambda_4}\Lambda_4(\overline{H}_e, \gamma_{\Lambda_{4,1}})\Big)N(1-\frac{N}{K_N}), \tag{1d}$$

where $\overline{H}_i$, $\overline{H}_e$, $\bar{C}$ and $\bar{N}$ are given in Subsection 7.1 of the Appendix.

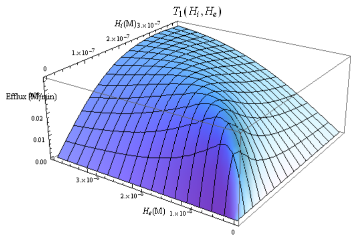
2.1 Intracellular proton dynamics (IPD) described by (1a):

Cells have various regulators to maintain their intracellular pH in the optimal range [8, 37]; membrane transporters are among those. In cancer cells the Warburg effect is accompanied by upregulation of NHE (Na^+ and H^+ exchanger) and NDBCE (Na^+ dependent Cl^--HCO_3^- exchanger) activities [48, 16, 34], which enables them to keep their $\mathrm{pH_i}$ relatively alkaline. The functions T_1 and T_2 (see Figure 1a and Figure 1b), modeled based on [49, 50, 5] and [19], represent the efflux of intracellular protons across the cell membrane due to NHE and NDBCE, respectively. Both T_1 and T_2 depend of course on the proton concentrations H_i and H_e. The countermechanism of intracellular acidification due to AE (Cl^--HCO_3^- or *a*nion *e*xchanger) is modeled by the function T_3 (see Figure 1c), which depends on H_i and H_e as well and relies on [49, 50, 5] and [19], too. For simplicity, we ignore the effects of the MC (monocarboxylate) transporter family.
The $\mathrm{pH_i}$ is also regulated by buffers and acid sequestration by intracellular organelles like mitochondria, lysosomes, nucleus, etc., [8, 37]. The corresponding loss is characterized by the function Q (see Figure 2a). The production rate of acid due to metabolic activity (mainly aerobic glycolysis) is represented by q_1 (see Figure 2b), which is a function of tissue vasculature v. For simplicity, we ignore the spatial dependence of v, hence it serves as a model parameter. ξ_t is a stochastic process which phenomenologically accounts for intracellular fluctuations affecting the proton dynamics. These may be due to: (i) uncertainty of the effects of various other biochemical process, (ii) random biochemical process like gene expression, random behavior of membrane transporters, etc.
Since we only account for protons expressed by the cancer cells, their production and cross-membrane flux must depend on the tumor cell density. As previously stated, cancer development and spread is controlled by both cell proliferation and movement, the latter being influenced by taxis and diffusion. In both cases the cells rely on glycolysis for energy production [46, 44, 3]. This in turn endorses the idea that acid dynamics is more pronounced at the tumor's invasion edge. The flux modulation function J shown in Figure 2c is designed to capture this behavior and it also characterizes the above mentioned dependence on the cell density. In Figure 2c, K_C denotes the carrying capacity of the tumor cell population; for the significance of the other parameters involved in the model we refer to Table 2.

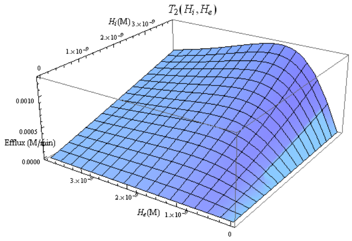
2.2 Extracellular proton dynamics (EPD) described by (1b):

Since the intracellular protons lost (or gained) via membrane transporters correspond to those gained (or lost) on the extracellular side, the functions T_1, T_2 and T_3 describing membrane transporters are the same with those in (1a), however with an opposite sign. The loss term with the rate q_2 represents the dissipation of protons through the blood vessels. Therefore, $q_2 > 0$ is dependent on the tissue vasculature v. The Laplace operator in the next term models diffusion of extracellular protons. Thereby, γ_D is the effective proton diffusion coefficient in the presence of densely packed cells.
The nonlinear operators $\nabla\cdot(g\nabla C)$ and $\nabla\cdot(h\nabla N)$ for non-negative functions g and h characterize the effect of proton repulsion from highly dense regions of cancer and normal cells towards less dense regions. These terms phenomenologically capture the accumulation of extracellular

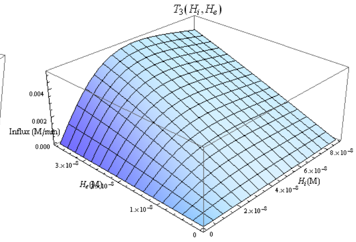
Figure 1: Functions representing NDCBE and NHE transporters effects



(a) T_1 as a function of H_i and H_e

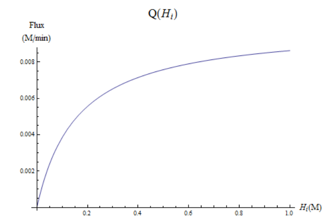


(b) T_2 as a function of H_i and H_e

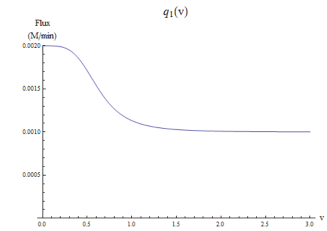


(c) T_3 as a function of H_i and H_e

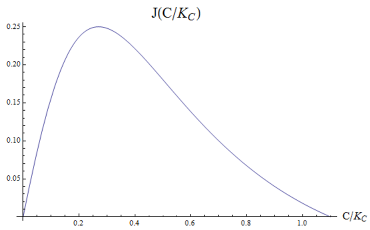
Figure 2: Functions used to model production and decay of protons



(a) Q as a function of H_i



(b) q_1 as a function of vascularity v



(c) J as a function of C/K_C

protons near the invasion front of the tumor. The movement of protons away from the tumor region can be, for instance, seen as the pushing of protons towards the areas of low cell density by the movement and proliferation of tumor cells. The latter reduces the interstitial (extracellular) space containing the protons, hence driving them towards the regions of lesser pressure. Alternatively (in order to account for such repulsive effects also in the normal tissue) one could conjecture the existence of a repulsive force due to the electrical potential of the interstitial space: the latter having a positive potential relative to the intracellular space [9], it generates a positive electric field pushing away the (positively charged) protons. [1] From this perspective, the choice of the flux ($h\nabla N$) is motivated by Planck's flux equation [23, (2.112)] $\mathcal{J} \propto H_e \nabla \phi$ where ϕ denotes the electrical potential. In our case the potential is taken to be proportional to the normal cell density N. Effects of density and orientation of cells on an electric field have been experimentally put in evidence e.g., in [32]. In our context it seems reasonable to assume the cells to form a more or less permeable 'barrier' for the electric field. Yet another reason for the repulsive effects could be that the protons buffered by the solution form larger molecules which are unable to easily diffuse into the normal tissue, as they do in a region with very few cells, hence the healthy tissue provides some kind of 'resistance'. The latter is supposed to increase with the gradient of the normal cell density.

The cancer cell repulsion coefficient g is a non-negative function of H_i, H_e and C, which is supposed to have the following properties: (i) it is directly proportional to the density of cancer cells and the concentration of extracellular protons. However, for fixed H_i and large values of C and H_e, it saturates to some upper asymptotic value (see Figure 3b and Figure 4b). (ii) As a function of H_i, for fixed values of C and H_e, it behaves like a Gamma function (see Figure 3a and Figure 4a).

The normal cell repulsion coefficient h is a non-negative function of H_e and N. It is directly proportional to the density of normal cells and the concentration of extracellular protons, however, for large values of N and H_e, it saturates to some upper asymptotic value (see Figure 3c).

[1] Voltage potentials and their influence on cancer development have been addressed e.g., in [10] (see also the references therein), but there seems to be no concrete reference to this conjecture of a proton-repulsive electric field. However, it is in a certain sense supported by the fact that cancer cells possess depolarized membrane potential [54], hence the protons could be pushed by further positive charges (like e.g., K^+).

Figure 3: Repulsion coefficients g and h as functions of their corresponding variables

(a) g as a function of H_i and $H_e = C$ (b) g as a function of H_e and C (c) h as a function of H_e and N

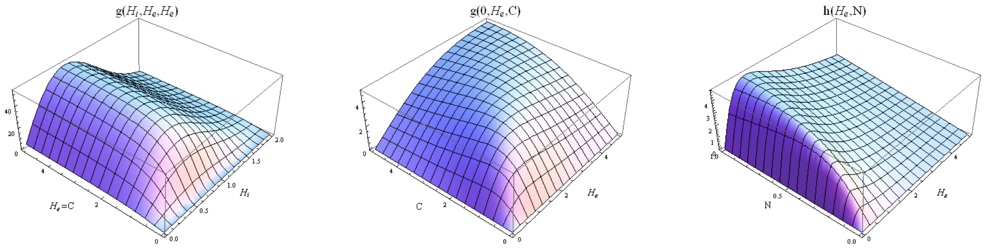
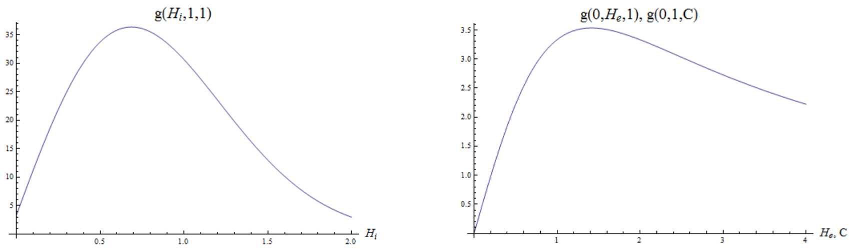


Figure 4: Repulsion coefficient g as a function of one of the variables H_i, H_e and C

(a) g as a function of H_i with $H_e = C = 1$ (b) g as a function of H_e (and C) with $H_i = 0$



2.3 Cancer cell population dynamics (CPD) described by (2c):

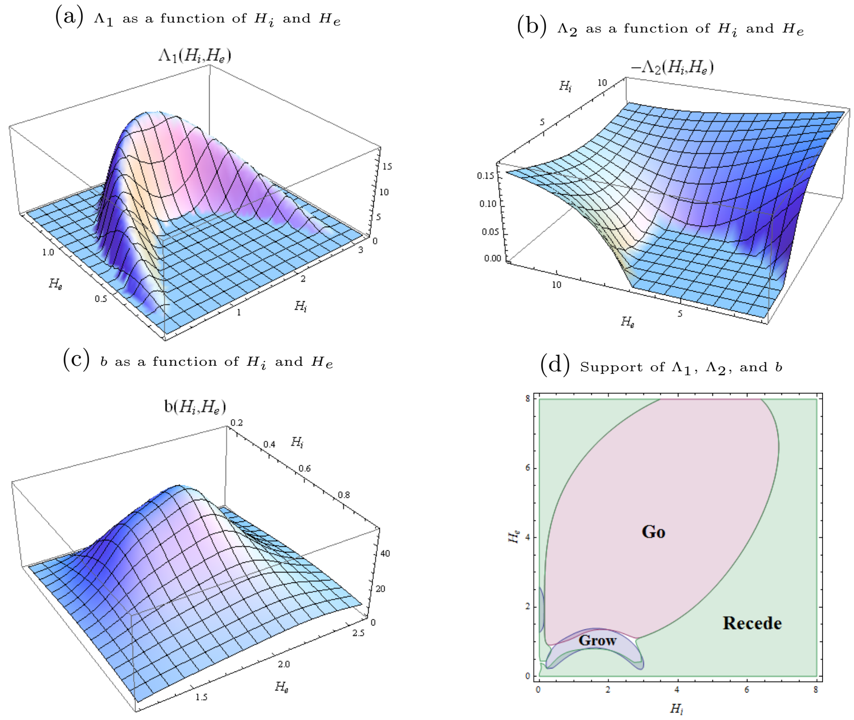
The growth of the cancer cell population is characterized by the intra-species competition term $C(1 - C/K_C)$, where K_C is the carrying capacity of the cancer cell population. This logistic-type growth is modulated by a proliferation function Λ_1 and a recession function Λ_2. Both functions depend on H_i, H_e and on the difference $H_e - H_i$. The proliferation function models the enhancement of mitosis if the intracellular region is favorably alkaline [48] and if the difference between the intra and extracellular pH is not too large. Similarly, the recession function models cell death due to highly acidic or too alkaline intracellular pH and highly acidic extracellular region [40, 17, 25]. Moreover, the supports of Λ_1 and Λ_2 are (nearly) disjoint, which qualitatively captures the behavior of cells either dying or growing. These features of Λ_1 and Λ_2 are depicted in Figures 5a and 5b.

The production of acid by the cells at the outer proximity of the tumor core causes degradation of stromal cells [48, 43, 38, 22]. On the other hand, the increased extracellular acidity enhances the movement of the cells at the tumor edge [48, 3, 36, 22]. This behavior is captured by the term modeling pH-taxis (i.e., the movement bias towards increasing H_e); here, however, the term involving $-\Delta H_e$ for a (signed) cross-diffusion of protons is neglected.

The taxis coefficient b is a non-negative function of both H_i and H_e: it is nonzero on a compact region of the (H_i, H_e) plane and attains its maximum when the difference $H_e - H_i$ is optimal, i.e. when a reversed pH gradient (still at a favorable level) is attained. Figure 5c depicts its qualitative properties. Moreover, its support is (nearly) disjoint from the supports of the proliferation and recession functions Λ_1 and Λ_2 respectively. Thus, it incorporates the *Go-or-Grow-or-Recede* (GGR) behavior of cancer cells [11, 13] (see Figure 5d). Finally, it is made to depend on the spatial variable such that the velocity is zero on the boundary and maximum at the center of the domain. This is merely a modeling simplification which allows us to retain the standard no-flux Neumann boundary condition.

The spreading behavior of cancer cells is modeled by a nonlinear diffusion operator. The diffusion coefficient a is inversely proportional to cell densities C and N and proportional to the product between $H_e - H_i$ and the cancer cell density C. It is uniformly bounded from below by a positive constant m_a and the support of $a - \mathrm{m}_a$ is a function of H_i, H_e and C with fixed values of N as shown in Figure 6. Additionally, the diffusion coefficient is uniformly bounded from above by some finite constant M_a. Before ending this subsection, we would like to remark that our choices of GGR functions and of the diffusion coefficient are phenomenological, only relying on qualitative biological facts, as no data were available for fitting. Hence, these particular choices are arguable and others are possible as well.

Figure 5: Go, grow and recede functions



(a) Λ_1 as a function of H_i and H_e

(b) Λ_2 as a function of H_i and H_e

(c) b as a function of H_i and H_e

(d) Support of Λ_1, Λ_2, and b

2.4 Normal cell population dynamics (NPD) described by (2d):

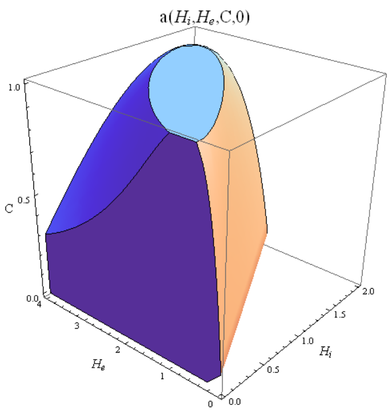
The dynamics of normal cells is essentially governed by growth and decay terms without spatial migration. The normal cell depletion is mainly due to interaction with cancer cells and with the extracellular acid. The first term in (2d) models the degradation of stromal cells by non-acidic proteolytic enzymes (like Cathepsin B, MMP, urokinase, etc..) secreted by tumor cells [38, 22, 29, 24, 42, 6] and is taken to be proportional to the cancer cell density. The next term models the decay due to acid [15, 35, 51] by a logistic degradation term modulated by the function Λ_3. We use this type of decay instead of the more common linear multiplicative one since we want the effect of acid to be maximum when the normal cell density is bounded away from its carrying capacity. The last term describes logistic growth modulated by the function $\Lambda_4(H_e, \gamma_{\Lambda_{4,1}})$. The growth function phenomenologically captures the effect of an open buffer system and the immunity response depending on the concentration of H_e [26, 45]. The parameter $\gamma_{\Lambda_{4,1}}$ controls the amplitude of the growth rate at the alkaline regions of the tissue. Both Λ_3 and Λ_4 are positive functions whose qualitative behavior is as shown in Figure 8.

3 Analysis of the stochastic multiscale model

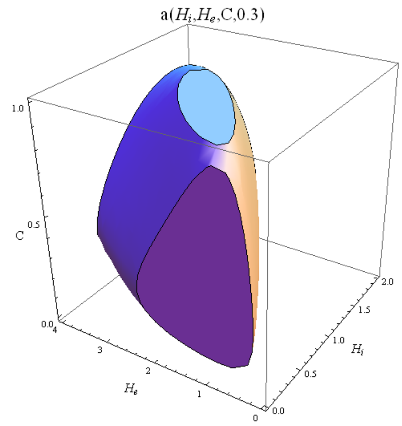
Let $I = (0,T] \subset \mathbb{R}_+$ be a finite time interval and $\mathfrak{D} \subset \mathbb{R}^n$ ($n \in \{1,2,3\}$) be an open bounded spatial domain with sufficiently smooth boundary. Furthermore, let $(\Omega, \mathcal{A}, \mathbb{P})$ be a complete probability space and $(\mathcal{A}_t)_{t\geq 0}$ be a normal filtration with $\mathfrak{N}$, the system of all $\mathbb{P}$-nullsets, contained in $\mathcal{A}_0$. Let $\xi : I \times \Omega \to \mathbb{R}$ be a $\mathbb{P}$-a.s. continuous, real-valued, $\mathcal{A}_t$-adapted, centered Gaussian process with independent increments and μ-Hölder continuous covariance function.

Figure 6: Support of $a - \mathrm{m}_a$ as a function of H_i, H_e, C and N. The normal cell density N is kept fixed at different increasing values.

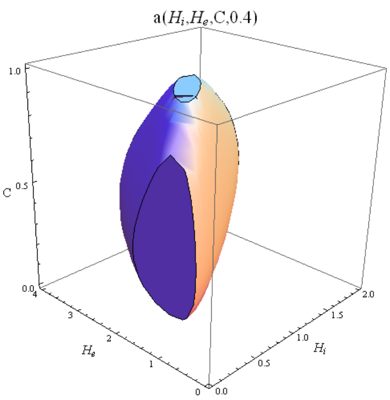
(a) a as a function of H_i, H_e and $C = 1$ with $N = 0$



(b) a as a function of H_i, H_e and $C = 1$ with $N = 0.3$



(c) a as a function of H_i, H_e and $C = 1$ with $N = 0.4$



(d) a as a function of H_i, H_e and $C = 1$ with $N = 0.5$

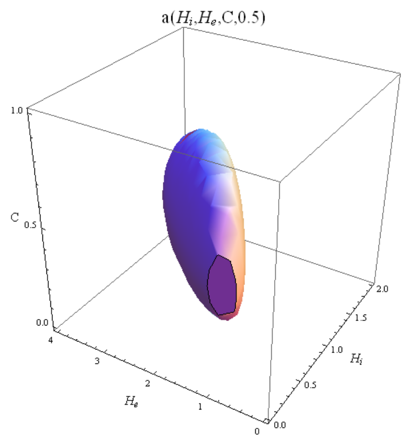
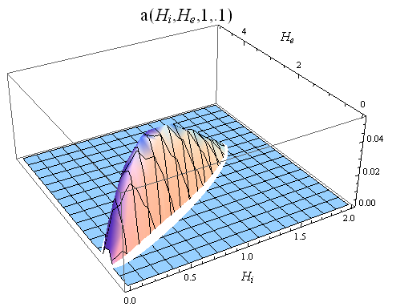


Figure 7: Diffusion coefficient a as a function of H_i, H_e and C, N, respectively.

(a) a as a function of H_i and H_e with $C = 1$, $N = .1$



(b) a as a function of C and N with $H_i = 1$, $H_e = 2$

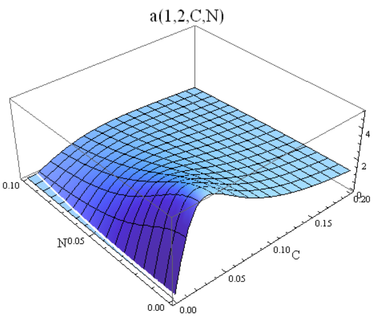
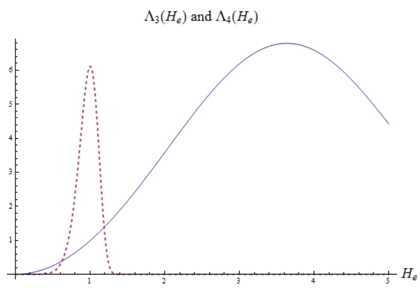


Figure 8: Growth and decay functions Λ_4 (dotted) and Λ_3 (solid line), respectively.



Then for each $\varsigma \in \Omega \backslash \mathfrak{N}$ we have the following non-dimensionalized system:

$$\frac{d}{dt} H_i = J(C)[-T_1 - T_2 + T_3 - Q + q_1] + \gamma_\xi \, J(C) H_i \xi_t, \qquad \text{in } I \times \mathfrak{D} \tag{2a}$$
$$H_i(0, \varsigma) = H_{i,0}(\varsigma), \qquad \text{in } \mathfrak{D}$$

$$\frac{\partial}{\partial t} H_e = J(C)[T_1 + T_2 - T_3] - q_2 H_e + \gamma_D \Delta H_e + \gamma_g \nabla \cdot \Big(g \nabla C \Big) + \gamma_h \nabla \cdot \Big(h \nabla N \Big), \qquad \text{in } I \times \mathfrak{D} \tag{2b}$$
$$H_e(0, \varsigma) = H_{e,0}(\varsigma), \qquad \text{in } \mathfrak{D}$$
$$\nabla H_e(\varsigma) \cdot \hat{n} = 0, \qquad \text{on } I \times \partial \mathfrak{D}$$

$$\frac{\partial}{\partial t} C = C(1 - C) \Big(\gamma_{\Lambda_1} \Lambda_1 + \gamma_{\Lambda_2} \Lambda_2 \Big) + \gamma_a \nabla \cdot \Big(a \nabla C \Big) - \gamma_b b \nabla H_e \cdot \nabla C, \qquad \text{in } I \times \mathfrak{D} \tag{2c}$$
$$C(0, \varsigma) = C_0(\varsigma), \qquad \text{in } \mathfrak{D}$$
$$\nabla C(\varsigma) \cdot \hat{n} = 0, \qquad \text{on } I \times \partial \mathfrak{D}$$

$$\frac{d}{dt} N = -\gamma_N C N + N(1 - N) \Big(- \gamma_{\Lambda_3} \Lambda_3 + \gamma_{\Lambda_4} \Lambda_4(\gamma_{\Lambda_{4,1}}) \Big), \qquad \text{in } I \times \mathfrak{D} \tag{2d}$$
$$N(0, \varsigma) = N_0(\varsigma). \qquad \text{in } \mathfrak{D}.$$

For the concrete rescaling relations used in the nondimensionalization we refer to Subsection 7.1 in the Appendix. To avoid overloading the notations we will omit in the writing the dependencies of the coefficients in the transport and (cross-)diffusion terms on the solution, but will keep these in mind everywhere in the following.

3.1 Assumptions about coefficients:

First we shall make some assumptions about the coefficients involved in the diffusion, repulsion. Let $1 < p < \infty$ and $s \in \mathbb{R}$. In the following $H_p^s(\mathfrak{D})$ denotes the Bessel potential space (see Definition 2 in the Appendix) and $W^{s,p}(\mathfrak{D})$ is the usual Sobolev space of non-integer exponent.

Model parameters Ξ: The parameters appearing in the model are represented by the vector $\Xi := (\Xi_R, \Xi_M)^T$. The two sub-vectors Ξ_R and Ξ_M are defined as follows:

$$\Xi_R := (\gamma_N, \gamma_{\Lambda_1}, \gamma_{\Lambda_2}, \gamma_{\Lambda_3}, \gamma_{\Lambda_4}, \gamma_{\Lambda_{4,1}}, \gamma_\xi)^T \in \mathbb{R}_+^7$$

consists of the growth and decay constants appearing in the reaction terms and

$$\Xi_M := (\gamma_D, \gamma_g, \gamma_h, \gamma_a, \gamma_b)^T \in \mathbb{R}_+^5$$

consists of the repulsion, diffusion and advection constants. As already indicated in the definition, Ξ_R and Ξ_M are strictly positive real numbers. For the functional relevance of the involved components, please refer to Table 2.

Properties of the repulsion coefficients $g(C, H_e, H_i)$ and $h(N, H_e)$:

1. $g(t) := g(C(t), H_e(t), H_i(t)) \in H_p^2(\mathfrak{D})$ whenever $C(t),\ H_e(t) \in H_p^2(\mathfrak{D})$, $t \in I$.
2. $h(t) := h(N(t), H_e(t)) \in H_p^2(\mathfrak{D})$ if $N(t),\ H_e(t) \in H_p^2(\mathfrak{D})$, $t \in I$.
3. g and h are uniformly bounded w.r.t. each of the independent variables t, x, and ω: $|g| \leq \mathrm{M}_g < \infty$ and $|h| \leq \mathrm{M}_h < \infty$.
4. $g(t)$ and $h(t)$ are Lipschitz continuous in $H_{2p}^1(\mathfrak{D})$ if $H_i(t), H_e(t), C(t), N(t) \in H_{2p}^1(\mathfrak{D})$.

In the following we will omit in the writing the dependence on t of the components of the solution vector $\mathbf{u} := [H_i,\ H_e,\ C,\ N]^T$ belonging to function spaces of the form $H_p^s(\mathfrak{D})$, $s > 0$.

Properties of the diffusion coefficient $a(H_i, H_e, C, N)$**:**

1. $0 < \mathrm{m}_a \leq a \leq \mathrm{M}_a < \infty$.
2. If H_e, H_i, C and $N \in H^1_{2p}(\mathfrak{D})$, then a belongs to $H^1_{2p}(\mathfrak{D})$, too.
3. a is Lipschitz continuous in $L^p(\mathfrak{D})$ if H_i, H_e, C and N are in $H^1_{2p}(\mathfrak{D})$, with $p > n$.

Properties of the go, grow and recede coefficients $b(H_i, H_e)$**,** $\Lambda_1(H_e, H_i)$ **and** $\Lambda_2(H_e, H_i)$**:**

1. $0 \leq b \leq \mathrm{M}_b$, $0 \leq \Lambda_1 \leq \mathrm{M}_{\Lambda_1}$, $|\Lambda_2| \leq \mathrm{M}_{\Lambda_2}$ and $\Lambda_2 \leq 0$, where M_b, M_{Λ_1}, and M_{Λ_2} are bounded constants.
2. If H_i and H_e belong to $H^1_{2p}(\mathfrak{D})$ then b, Λ_1 and Λ_2 belong to $H^1_{2p}(\mathfrak{D})$, as well.
3. b is Lipschitz continuous in $L^p(\mathfrak{D})$ if H_i, H_e, C and N are in $H^1_{2p}(\mathfrak{D})$, with $p > n$.

Properties of the reaction terms $T(H_i, H_e)$ **and** $Q(H_i)$**:**

1. $|T| \leq \mathrm{M}_T < \infty$, $0 \leq Q \leq \mathrm{M}_Q < \infty$.
2. If both H_i and H_e are in $H^1_{2p}(\mathfrak{D})$ then T and Q are in $H^1_{2p}(\mathfrak{D})$.
3. T and Q are Lipschitz continuous in $H^1_{2p}(\mathfrak{D})$ norm if the corresponding dependent functions H_e and H_i are in $H^1_{2p}(\mathfrak{D})$.

Properties of the growth and decay terms $\Lambda_3(H_e)$ **and** $\Lambda_4(H_e)$**:**

1. $0 \leq \Lambda_3 \leq \mathrm{M}_{\Lambda_3} < \infty$, $0 \leq \Lambda_4 \leq \mathrm{M}_{\Lambda_4} < \infty$.
2. If H_e is in $H^1_{2p}(\mathfrak{D})$ then Λ_3 and Λ_4 are in $H^1_{2p}(\mathfrak{D})$.
3. Λ_3 and Λ_4 are Lipschitz continuous in $H^1_{2p}(\mathfrak{D})$ norm if H_e is in $H^1_{2p}(\mathfrak{D})$.

Properties of the flux modulation function $J(C)$**:**

1. $J \in L^\infty(\mathfrak{D})$.
2. If C is in $H^1_{2p}(\mathfrak{D})$ then J is in $H^1_{2p}(\mathfrak{D})$, with $\|J\|_{H^1_{2p}(\mathfrak{D})} \leq \mathrm{M}_J(\mathrm{k}_C)$. Here $M_J(\mathrm{k}_C)$ represents a positive and polynomial order function of k_C with k_C being a constant occurring in the following sections below.
3. J is Lipschitz continuous in the $H^1_{2p}(\mathfrak{D})$ norm if C is in $H^1_{2p}(\mathfrak{D})$.

Further properties of the above functions: The functions J, T_j $(j = 1, 2, 3)$, and Q are such that (with the notations to follow) $R_1(H_i, \cdot, \cdot) > 0$ in a small neighborhood of $H_i = 0$ and $R_1(0, \cdot, \cdot) = 0$.

We will use the following notations for the reaction and source terms involved in our model:

$$T(H_i, H_e) := T_1(H_i,\ H_e) + T_2(H_i,\ H_e) - T_3(H_i, H_e) \tag{3a}$$
$$R_1(H_i, H_e, C) := J(C)[-T(H_i, H_e) - Q + q_1] \tag{3b}$$
$$R_2(H_i,\ H_e) := J(C)T(H_i, H_e) \tag{3c}$$
$$R_3(H_i, C, N) := C(1 - C)\Big(\gamma_{\Lambda_1}\Lambda_1 + \gamma_{\Lambda_2}\Lambda_2\Big) \tag{3d}$$
$$R_4(H_e, C, N) := -\gamma_N CN + \Big(-\gamma_{\Lambda_3}\Lambda_3 + \gamma_{\Lambda_4}\Lambda_4\Big)N(1 - N) \tag{3e}$$

Using the above assumptions, the proof of the following lemma is straightforward.

Lemma 3.1 (Lipschitz continuity of R_1, R_2 and R_3)**.** *Let H_i, H_e, C and N be in $H^1_{2p}(\mathfrak{D})$, with $p > n$. Then R_1 and R_2 are Lipschitz continuous in $H^1_{2p}(\mathfrak{D})$, and R_3 is Lipschitz continuous in $L^p(\mathfrak{D})$.*

3.2 Generating operator:

With the previous notation $\mathbf{u} := [H_i,\ H_e,\ C,\ N]^T$, define the operator $\mathbb{A}(\mathbf{u})$ as

$$\mathbb{A}(\mathbf{u}) := \begin{bmatrix} A_1 & 0 & 0 & 0 \\ 0 & A_2 & 0 & 0 \\ 0 & 0 & B_1 & B_2 \\ 0 & 0 & 0 & B_3 \end{bmatrix} = \begin{bmatrix} \mathbf{A} & \mathbf{0} \\ \mathbf{0} & \mathbf{B} \end{bmatrix} \tag{4}$$

with

$$\mathbf{A} := \begin{bmatrix} A_1 & 0 \\ 0 & A_2 \end{bmatrix}$$

$$A_1(C) := -J(C)\xi_t$$

$$A_2(C,\ N) := \gamma_{_N} C + (\Lambda_3 - \Lambda_4)(1 - N)$$

$$\mathbf{B} := \begin{bmatrix} B_1 & B_2 \\ 0 & B_3 \end{bmatrix}$$

$$B_1 := q_2 - \gamma_{_D} \Delta$$

$$B_2(C,\ H_e) := -\nabla \cdot (g(C, H_e)\nabla)$$

$$B_3(C,\ H_e,\ N) := -\nabla \cdot (a(C,\ H_e,\ N)\nabla) + q_3$$

where q_3 is an arbitrary positive real constant introduced to render B_3 to be an injective operator. The constants involved in the vectors $\Xi_{_R}$ and $\Xi_{_M}$ above are from now on absorbed in the respective diffusion, taxis, repulsion etc. coefficients. The original notation for these coefficients will be preserved in order not to overload the presentation.

3.2.1 Uniformly continuous operators and their domains:

Lemma 3.2. *Let $N(\omega)$, $C(\omega)$, and $H_e(\omega)$ be in $C([0,T]; H^2_p(\mathfrak{D}))$ for every $\omega \in \Omega$. Then $A_2(\omega, t) : H^2_p(\mathfrak{D}) \to H^2_p(\mathfrak{D})$, $p \in (n,\ \infty]$, is a bounded linear operator. Moreover, it generates the following uniformly continuous semigroup*

$$\mathrm{e}^{-\int_0^t A_2(\omega,s)ds} = \mathrm{e}^{-\int_0^t \gamma_{_N} C(\omega) + (\Lambda_3(\omega) - \Lambda_4(\omega))(1 - N(\omega))ds}, \quad t \in [0,T]$$

Proof. Indeed, since $H^2_p(\mathfrak{D})$ is a Banach algebra for $p > n$, for any $w(\omega,t) \in H^2_p(\mathfrak{D})$ we get that

$$\begin{aligned} \|A_2(\omega,t)w\|_{H^2_p(\mathfrak{D})} &= \|[\gamma_{_N} C(\omega) + (\Lambda_3(\omega) - \Lambda_4(\omega))(1 - N(\omega))]w\|_{H^2_p(\mathfrak{D})} \\ &\leq \gamma_{_N} \mathrm{k}_{_C} + \mathrm{k}_{_{\Lambda_{3,4}}}(1 + \mathrm{k}_{_N})\|w\|_{H^2_p(\mathfrak{D})}. \end{aligned}$$

Hence,

$$\|A_2(\omega,t)\|_{\mathcal{L}(H^2_p(\mathfrak{D}))} \leq \mathrm{k}_{_{A_2}} < \infty, \qquad \text{a.s. } \forall t \in [0,T]. \tag{5}$$

where $\mathcal{L}(H^2_p(\mathfrak{D}))$ denotes the space of bounded linear operators form $H^2_p(\mathfrak{D})$ into itself, the constants $\mathrm{k}_{_C}(t)$, $\mathrm{k}_{_{\Lambda_{3,4}}}(t)$, and $\mathrm{k}_{_N}(t)$ are upper bounds (in $H^2_p(\mathfrak{D})$ [2]) for C, H_e, and N, respectively, and $\mathrm{k}_{_{A_2}} := \gamma_{_N} \mathrm{k}_{_C} + \mathrm{k}_{_{\Lambda_{3,4}}}(1 + \mathrm{k}_{_N})$, with

$$\mathrm{k}_{_C} := \sup_{t\in[0,T]} \mathrm{k}_{_C}(t), \quad \mathrm{k}_{_{\Lambda_{3,4}}} := \sup_{t\in[0,T]} \mathrm{k}_{_{\Lambda_{3,4}}}(t), \quad \mathrm{k}_{_N} := \sup_{t\in[0,T]} \mathrm{k}_{_N}(t).$$

Now for the semigroup claim, let $w(\omega,t) = \mathrm{e}^{-\int_0^t A_2(\omega,s)ds} v$. Then it is easy to see the semigroup property and the following differentiability property:

$$\frac{d}{dt} w(\omega,t) = -A_2(\omega,t)w(\omega,t).$$

The following estimates are easily obtained:

$$\|\mathrm{e}^{-\int_0^t A_2(\omega,s)ds}\|_{\mathcal{L}(H^2_p(\mathfrak{D}))} \leq \mathrm{e}^{\mathrm{k}_{A_2} T}, \tag{6a}$$

$$\|\mathrm{e}^{-\int_0^t A_2(\omega,s)ds} - 1\|_{\mathcal{L}(H^2_p(\mathfrak{D}))} \leq \sum_{k=1}^{\infty} \frac{t^k \|A_2(\omega,t)\|^k_{\mathcal{L}(H^2_p(\mathfrak{D}))}}{k!} \leq T\, \mathrm{k}_{_{A_2}} \mathrm{e}^{T \mathrm{k}_{_{A_2}}} \tag{6b}$$

$$\|\mathrm{e}^{-\int_0^t A_2(\omega,s)ds} - \mathrm{e}^{-\int_0^r A_2(\omega,s)ds}\|_{\mathcal{L}(H^2_p(\mathfrak{D}))} \leq |t - r| \mathrm{k}_{_{A_2}} \mathrm{e}^{2T \mathrm{k}_{_{A_2}}}. \tag{6c}$$

So the uniform continuity follows from the boundedness of A_2. ■

[2] In the following, depending on the context, the norms with respect to which the upper bounds $\mathrm{k}_{_C}(t)$, $\mathrm{k}_{_{\Lambda_{3,4}}}(t)$, and $\mathrm{k}_{_N}(t)$ are represented may differ from $H^2_p(\mathfrak{D})$. In general, the norms are taken with respect $H^s_p(\mathfrak{D})$ with $s \in \mathbb{R}$ such that either $H^s_p(\mathfrak{D}) \hookrightarrow H^2_p(\mathfrak{D})$ or $H^s_p(\mathfrak{D}) \hookrightarrow H^1_{2p}(\mathfrak{D})$ or $H^s_p(\mathfrak{D}) \hookrightarrow L^\infty(\mathfrak{D})$.

Lemma 3.3. *For $T \in (0,\infty)$, let $C \in L^\infty(\Omega; C([0,T]; H_p^{2\beta'}(\mathfrak{D})))$ with $\beta' > \frac{1}{2}$ and $\xi \in L^2(\Omega; C([0,\infty); \mathbb{R}))$ be a Gaussian process with μ-Hölder continuous covariance function ($0 < \mu < \frac{1}{2}$). Then for each $\omega \in \Omega$, $A_1(\omega,t) : H^1_{2p}(\mathfrak{D}) \to H^1_{2p}(\mathfrak{D})$, $p > n$, is a bounded linear operator. Moreover, for each $\omega \in \Omega$ it generates the following uniformly continuous semigroup:*

$$\mathrm{e}^{-\int_0^t A_1(\omega,s)ds} = \mathrm{e}^{\int_0^t J(C(\omega,s))\xi_s(\omega)ds}$$

Proof. First fix $\omega \in \Omega$, then the mapping $t \mapsto \xi(\omega,t)$ belongs to $C([0,T],\mathbb{R})$. So

$$\begin{aligned}\|A_1(\omega,t)w\|_{H^1_{2p}(\mathfrak{D})} = \|\xi_t(\omega)J(C(\omega,t))w\|_{H^1_{2p}(\mathfrak{D})} &= |\xi_t(\omega)|\|J(C(\omega,t))\|_{H^1_{2p}(\mathfrak{D})}\|w\|_{H^1_{2p}(\mathfrak{D})} \\ &\leq \mathrm{M}_J(\mathrm{k}_C)|\xi_t(\omega)|\|w\|_{H^1_{2p}(\mathfrak{D})}\end{aligned}$$

Hence

$$\|A_1(\omega,t)\|_{\mathcal{L}\left(H^1_{2p}(\mathfrak{D})\right)} \leq \mathrm{k}_{A_1}(\omega,t) \tag{7}$$

$$\stackrel{\mathbb{E}}{\Rightarrow} \|A_1(t)\|_{L^2\left(\Omega;\mathcal{L}(H^1_{2p}(\mathfrak{D}))\right)} \leq \mathrm{k}_{A_1}, \tag{8}$$

where

$$\begin{aligned}&\mathrm{k}_{A_1}(\omega,t) := |\xi_t(\omega)|\mathrm{M}_J, \quad \mathrm{k}_{A_1} := \mathrm{k}_{\sigma_T}\mathrm{M}_J, \qquad \mathrm{M}_J := \mathrm{M}_J(\mathrm{k}_C + \mathrm{k}_C^2), \\ &\mathrm{k}_{\sigma_T} := \sup_{t\in[0,T]} \sigma(t), \qquad \sigma(t) = \mathbb{E}(|\xi_t(\omega)|^2)^{\frac{1}{2}}.\end{aligned}$$

Now the semigroup claim follows like in the previous case for each $\omega \in \Omega$ fixed, with the following estimates (using Lemma 7.3):

$$\|\mathrm{e}^{-\int_0^t A_1(s)ds}\|_{L^2\left(\Omega;\mathcal{L}(H^1_{2p}(\mathfrak{D}))\right)} \leq \sqrt{\mathrm{k}_{A_1}}\mathrm{e}^{\mathrm{k}^2_{A_1}}, \tag{9a}$$

$$\|\mathrm{e}^{-\int_0^t A_1(s)ds} - 1\|_{L^2\left(\Omega;\mathcal{L}(H^1_{2p}(\mathfrak{D}))\right)} \leq \sum_{k=1}^{\infty} \frac{t^k\|A_1(\omega,t)\|^k_{\mathcal{L}(H^1_{2p}(\mathfrak{D}))}}{k!} \leq \sqrt{t\,\mathrm{k}_{A_1}}\mathrm{e}^{\mathrm{k}^2_{A_1}}, \tag{9b}$$

$$\|\mathrm{e}^{-\int_0^t A_1(s)ds} - \mathrm{e}^{-\int_0^r A_1(s)ds}\|_{L^2\left(\Omega;\mathcal{L}(H^1_{2p}(\mathfrak{D}))\right)} \leq (\mathrm{k}_{\sigma_T}|t-r| + T|t-r|^\mu)\sqrt{\mathrm{k}_{A_1}}\mathrm{e}^{2\mathrm{k}^2_{A_1}}. \tag{9c}$$

■

3.2.2 Sectorial operators:

Let $H_p^s(\mathfrak{D})$ denote as before the L^p-Bessel potential space with $s \in \mathbb{R}$ and $1 < p < \infty$. In order to characterize the domains of the operators involved in the aanalysis below, we need the following subspace of $H_p^s(\mathfrak{D})$ (which can be identified with the Sobolev space $W^{s,p}(\mathfrak{D})$, see Remark 3 in Subsection 7.3):

$$H^2_{p,N} := \left\{u \in H^2_p(\mathfrak{D}) : \frac{\partial u}{\partial \nu} = 0\right\}.$$

Sectorial property of B_1

Consider the operator $B_1 := q_2 - \gamma_D\Delta$, with $D(B_1) = H^2_{p,N}$. We would like to find out whether it generates a semigroup on $L^p(\mathfrak{D})$. Now we get the following sectorial property of B_1 (see Definition 1 in the Appendix):

Lemma 3.4. *The operator B_1 is a sectorial operator with spectral angle $\kappa_{B_1} < \frac{\pi}{2}$. The resolvent $R_\lambda(B_1)$ satisfies the following inequalities:*

$$\begin{aligned}&\|R_\lambda(B_1)\|_{\mathcal{L}(L^p(\mathfrak{D}))} \leq \frac{1}{|Re\ \lambda| + q_2}, \quad Re\ \lambda \leq 0 \\ &\|R_\lambda(B_1)\|_{\mathcal{L}(L^p(\mathfrak{D}))} \leq \frac{M_{B_1}}{|\lambda|}, \quad Re\ \lambda \leq 0, \quad \lambda \neq 0,\end{aligned} \tag{10}$$

where $M_{B_1} := \frac{\gamma_D np}{2\delta_{B_1}\sqrt{p-1}} + 2$.

Proof. Firstly, due to Theorem 2.4.1.3 in Grisvard [18] we get that, for $-\lambda$ large enough, $B_1 - \lambda$ is a bijection from $H^2_{p,N}(\mathfrak{D})$ onto $L^p(\mathfrak{D})$. This immediately gives us that $\mathcal{R}(B_1 - \lambda) = L^p(\mathfrak{D})$. Additionally, we get that B_1 is a closed operator. Secondly, since B_1 is also accretive (see [53] Lemma 2.3) we get that B_1 is m-accretive. This implies that B_1 is non-negative. Thirdly, since $L^p(\mathfrak{D})$ is reflexive, we also get that B_1 is densely defined. Finally, from [53] Lemma 2.3, we get that for all $u \in L^p(\mathfrak{D})$,

$$\frac{|\mathrm{Im}\ \langle B_1 u, u^*\rangle|}{|\mathrm{Re}\ \langle B_1 u, u^*\rangle|} \leq \frac{\gamma_{_D} np}{2\delta_{_{B_1}}\sqrt{p-1}} < \infty.$$

where $\delta_{_{B_1}} := \min(q_2, \gamma_{_D})$ and $u^* \in F(u)$, i.e. u^* is an element of the duality set $F(u) := \{u^* \in (L^p(\mathfrak{D}))' : \langle u^*, u\rangle = \|u\|^2_{L^p(\mathfrak{D})} = \|u^*\|^2_{(L^p(\mathfrak{D}))'}\}$ of u. This implies that the numerical range $W(B_1) := \{\langle B_1 u, u'\rangle : u \in D(B_1), \|u\| = 1, u' \in F(u)\}$ (see [33]) of B_1 is contained in the sector of angle $\kappa_{_{B_1}} \leq \arctan\left(\frac{\gamma_{_D} np}{2\delta_{_{B_1}}\sqrt{p-1}}\right) < \frac{\pi}{2}$. Thus B_1 is a sectorial operator with spectral angle $\kappa_{_{B_1}} < \frac{\pi}{2}$. The estimates are again a consequence of Proposition 2.1 [53]. It is important to observe here that the sector angle $\kappa_{_{B_1}}$ and the constant M_{B_1} are independent of $\omega \in \Omega$. ■

Sectorial property of B_3

Consider the operator $B_3 := q_3 - \nabla \cdot (a\nabla)$ with $D(B_3) = H^2_{p,N}$. Like in the case of the operator B_1, we want to find out if B_3 generates a semigroup on $L^p(\mathfrak{D})$. The following Lemma gives its sectorial property.

Lemma 3.5. *Let $a(\omega, t) \in H^1_{2p}(\mathfrak{D})$ be Lipschitz continuous such that $\mathrm{M}_a \geq a \geq \mathrm{m}_a > 0$ for all $t \geq 0$ and $\omega \in \Omega$. Then the operator $B_3 := -\nabla \cdot (a(\omega, t)\nabla) + q_3$ is a sectorial operator on $L^p(\mathfrak{D})$ with a uniform spectral angle $\kappa_{_{B_3}} < \frac{\pi}{2}$ for all $t \geq 0$ and $\omega \in \Omega$. Its resolvent satisfies the following estimates:*

$$\begin{aligned} \|R_\lambda(B_3)\|_{\mathcal{L}(L^p(\mathfrak{D}))} &\leq \frac{1}{|Re\ \lambda| + q_3}, \quad Re\ \lambda \leq 0, \\ \|R_\lambda(B_3)\|_{\mathcal{L}(L^p(\mathfrak{D}))} &\leq \frac{M_{B_3}}{|\lambda|}, \quad Re\ \lambda \geq 0, \quad \lambda \neq 0, \end{aligned} \tag{11}$$

where, $M_{B_3} := \frac{\mathrm{M}_a\, n\, p}{2\delta_{_{B_3}}\sqrt{p-1}} + 2$, $\delta_{_{B_3}} := \min(q_3, \mathrm{m}_a)$.

Proof. Since $a \in H^1_{2p}(\mathfrak{D})$ and Lipschitz continuous, we can again apply Theorem 2.4.1.3 from Grisvard [18] and get that $B_3 - \lambda$ is a bijection from $H^2_{p,N}(\mathfrak{D})$ onto $L^p(\mathfrak{D})$ for $-\lambda$ large enough. Therefore, by the same arguments as in Lemma 3.4 we get that B_3 is a sectorial operator with spectral angle $\kappa_{_{B_3}} \leq \arctan\left(\frac{\mathrm{M}_a np}{2\delta_{_{B_3}}\sqrt{p-1}}\right) < \frac{\pi}{2}$ and the claimed estimates for its resolvent hold. Again it is crucial to observe here that the sector angle $\kappa_{_{B_3}}$ and the constant M_{B_3} are independent of $\omega \in \Omega$. ■

Sectorial property of B

Using perturbation results we now obtain the sectorial property of the matrix operator $\mathbf{B}$.

Theorem 3.6. *Consider the operator B_2 in (4) and let $g(\omega) \in B([0, T]; H^r_p(\mathfrak{D}))$ (i.e., g is uniformly bounded, see Definition 4), for every $\omega \in \Omega$ with $T > 0$ and $r \geq 1 + \frac{n}{2p}$ and $p > n$. Then the operator $\mathbf{B}$ is sectorial on $L^p(\mathfrak{D}) \times L^p(\mathfrak{D})$, with spectral angle $\kappa_{\mathbf{B}} \leq \max(\kappa_{_{B_1}}, \kappa_{_{B_3}}) < \frac{\pi}{2}$. Its resolvent satisfies the following:*

$$\begin{aligned} R_\lambda(\mathbf{B}) &= \begin{bmatrix} R_\lambda(B_1) & R_\lambda(B_1) B_2 B_3^{-1} B_3 R_\lambda(B_3) \\ 0 & R_\lambda(B_3) \end{bmatrix} \\ \|R_\lambda(B_1)\|_{\mathcal{L}(L^p(\mathfrak{D}) \times L^p(\mathfrak{D}))} &\leq \frac{M_{\mathbf{B}}}{|\lambda|}, \quad \lambda \in \{\Sigma_{\kappa_{\mathbf{B}}} \cup 0\}^c, \end{aligned} \tag{12}$$

where $M_{\mathbf{B}} := \max\Big(M_{B_1}, M_{B_3} + M_{B_1}(1 + M_{B_3})\|B_2 B_3^{-1}\|_{L^p(\mathfrak{D})}\Big)$. Moreover, its domain is given by

$$D(\mathbf{B}) = D(B_1) \times D(B_3) = H^2_{p,N} \times H^2_{p,N}$$

Proof. First note that $B_1 = -\gamma_D \Delta + q_2$ is a sectorial operator on $L^p(\mathfrak{D})$ with spectral angle $\kappa_{B_1} < \frac{\pi}{2}$ and domain $D(B_1) = H^2_{p,N}(\mathfrak{D})$. The operator $B_3 = -\nabla \cdot (a\nabla u) + q_3$ is sectorial, too, with spectral angle $\kappa_{B_3} < \frac{\pi}{2}$ and domain $D(B_3) = H^2_{p,N}(\mathfrak{D})$.
Now, if $B_2 \in \mathcal{L}(D(B_3); L^p(\mathfrak{D}))$ then by Theorem 2.16 [53] we get that $\mathbf{B}$ is a sectorial operator of $L^p(\mathfrak{D}) \times L^p(\mathfrak{D})$ with domain $D(\mathbf{B}) = H^2_{p,N} \times H^2_{p,N}$. To this end we let $u \in D(B_3)$. Then

$$\begin{aligned} \|\nabla \cdot (g(\omega,t)\nabla u)\|_p &\leq \|\nabla g(\omega,t) \cdot \nabla u\|_p + \|g\|_\infty \|\Delta u\|_p \\ &\leq \|\nabla g(\omega,t)\|_{2p} \|\nabla u\|_{2p} + \|g(\omega,t)\|_\infty \|u\|_{H^2_p(\mathfrak{D})} \\ &\leq \mathrm{k}_{\mathfrak{D},p} \|g(\omega,t)\|_{H^r_p(\mathfrak{D})} \|u\|_{H^2_p(\mathfrak{D})} + \|g(\omega,t)\|_{H^r_p(\mathfrak{D})} \|u\|_{H^2_p(\mathfrak{D})} \\ &\leq \mathrm{k}_{\mathfrak{D},p} \|g(\omega)\|_{B([0,T];H^r_p(\mathfrak{D}))} \|u\|_{H^2_p(\mathfrak{D})} < \infty, \end{aligned} \tag{13}$$

where we used the embeddings $H^r_p(\mathfrak{D}) \hookrightarrow H^1_{2p}(\mathfrak{D})$ and $H^r_p(\mathfrak{D}) \hookrightarrow L^\infty(\mathfrak{D})$ (see [4] and [53], respectively). Thus $D(B_3) \subset D(B_2)$ and as a consequence B_2 is a bounded linear operator from $D(B_3)$ to $L^p(\mathfrak{D})$. This implies that $\big(\mathbf{B}, D(\mathbf{B})\big)$ is densely defined and a closed operator. Moreover, since Re $\langle B_2 u^2, (u^2)^*\rangle \geq 0$ for $u^2 \in D(B_2)$ and $(u^2)^* \in F(u^2)$, for $\mathbf{u} = (u^1, u^2)^T \in D(B_1) \times D(B_3)$ with $\mathbf{u}^* \in F(\mathbf{u})$ we have that

$$\begin{aligned} \mathrm{Re}\, \langle \mathbf{Bu}, \mathbf{u}^* \rangle &= \mathrm{Re}\, \langle B_1 u^1, (u^1)^* \rangle + \mathrm{Re}\, \langle B_2 u^2, (u^2)^* \rangle + \mathrm{Re}\, \langle B_3 u^2, (u^2)^* \rangle \\ &\geq \delta_{B_1}(u^1, (u^1)^*) + \delta_{B_3}(u^2, (u^2)^*) > 0. \end{aligned}$$

and

$$\begin{aligned} \frac{|\mathrm{Im}\, \langle \mathbf{Bu}, \mathbf{u}^* \rangle|}{|\mathrm{Re}\, \langle \mathbf{Bu}, \mathbf{u}^* \rangle|} &\leq \frac{|\mathrm{Im}\, \langle B_1 u^1, (u^1)^* \rangle| + |\mathrm{Im}\, \langle B_2 u^2, (u^2)^* \rangle| + |\mathrm{Im}\, \langle B_3 u^2, (u^2)^* \rangle|}{|\mathrm{Re}\, \langle B_1 u^1, (u^1)^* \rangle + \mathrm{Re}\, \langle B_2 u^2, (u^2)^* \rangle + \mathrm{Re}\, \langle B_3 u^2, (u^2)^* \rangle|} \\ &\leq \frac{(\gamma_D + \mathrm{M}_g + \mathrm{M}_a) np}{(\delta_{B_1} + \delta_{B_3}) 2\sqrt{p-1}} < \infty. \end{aligned}$$

Thus $\mathbf{B}$ is m-accretive and its numerical range $W(\mathbf{B})$ is contained in a sector of angle $\arctan\left(\frac{(\gamma_D + \mathrm{M}_g + \mathrm{M}_a)np}{(\delta_{B_1} + \delta_{B_3})2\sqrt{p-1}}\right) < \frac{\pi}{2}$. Thus $\mathbf{B}$ is a sectorial operator with spectral angle $\kappa_{\mathbf{B}} < \frac{\pi}{2}$. The resolvent estimate follows directly from the matrix column norm and the resolvent estimates of B_1 (see (10)) and B_3 (see (11)). ■

Corollary 1. *For every $t \in [0,T]$ and $\omega \in \Omega$, the operator $-\mathbf{B}(\omega,t)$ defined above generates the analytic semigroup $\mathrm{e}^{-z\mathbf{B}(\omega,t)}$ on $\mathcal{L}(L^p(\mathfrak{D}) \times L^p(\mathfrak{D}))$, fulfilling the following properties:*

1. *For every fixed $t \in [0,T]$ and $\omega \in \Omega$, the mapping $z \mapsto \mathrm{e}^{-z\mathbf{B}(\omega,t)} \in \mathcal{L}(L^p(\mathfrak{D}) \times L^p(\mathfrak{D}))$ is an analytic function of $z \in \Sigma_{\frac{\pi}{2}-\kappa_{\mathbf{B}}}$.*
2. *For every $\kappa' > \kappa_{\mathbf{B}}$, the semigroup is uniformly bounded with respect to $z \in \overline{\Sigma}_{\frac{\pi}{2}-\kappa'} - 0$, i.e.*
$$\|\mathrm{e}^{-z\mathbf{B}(\omega,t)}\|_{\mathcal{L}(L^p(\mathfrak{D}) \times L^p(\mathfrak{D}))} \leq \mathrm{M}_{\kappa'}.$$
The upper bound $\mathrm{M}_{\kappa'}$, though it may depend on $\overline{\Sigma}_{\frac{\pi}{2}-\kappa'} \subseteq \Sigma_{\frac{\pi}{2}-\kappa_{\mathbf{B}}}$, is independent of t and ω.
3. *For every fixed $t \in [0,T]$ and $\omega \in \Omega$, the mapping $z \mapsto \mathrm{e}^{-z\mathbf{B}(\omega,t)}$ is strongly continuous at 0, i.e. $\mathrm{e}^{-z\mathbf{B}} \to 1$ as $z \to 0$ for all $z \in \overline{\Sigma}_{\kappa_{\mathbf{B}}} - 0$. The constant $\mathrm{M}_{\kappa'} \geq 1$ is uniform for all $t \in [0,T]$ and $\omega \in \Omega$.*

Proof. Due to the sectorial property of $\mathbf{B}(\omega,t)$, the resolvent estimate (12), and the denseness of $D(\mathbf{B}(\omega,t)) \subset \mathbf{X}$, we can apply Theorem 5.2 of Pazy [33] to get the required claim. ■

This allows us to define the two parameter semigroup $U_{\mathbf{B}}(t,s)$, for all $t \geq s \geq 0$, called the *evolution operator*. It serves us to represent the mild solution to the system of equations (2) which will eventually turn out to be the strong solution to the abstract Cauchy problem (20) below.

4 Construction of local solutions:

Let

$$H^{2\beta'}_{p,(N)}(\mathfrak{D}) := \begin{cases} H^{2\beta'}_p(\mathfrak{D}), & \text{if } 0 \le \beta' < \frac{p+1}{2p} \\ H^{2\beta'}_{p,N}(\mathfrak{D}), & \text{if } \frac{p+1}{2p} < \beta' \le 1, \end{cases}$$

then define $Z_\alpha := H^{2\alpha}_{p,(N)}(\mathfrak{D})$ for $\alpha \in [0,1]$, $Z := H^2_p(\mathfrak{D})$, and $Y := H^1_{2p}(\mathfrak{D})$. Now the product space $\mathbf{Z}$ is defined as:

$$\begin{aligned} &\mathbf{Z} := H^1_{2p}(\mathfrak{D}) \times H^1_{2p}(\mathfrak{D}) \times H^{2\beta'}_{p,(N)}(\mathfrak{D}) \times H^{2\beta'}_{p,(N)}(\mathfrak{D}) \\ \Leftrightarrow \quad &Z^1 \times Z^2 \times Z^3 \times Z^4 := Y \times Y \times Z_{\beta'} \times Z_{\beta'}. \end{aligned}$$

Let $\mathbf{u} := (u^1, u^2, u^3, u^4)^T$, and $k \in \{1,2,3,4\}$, then we define the following spaces (see Definitions 4 and 5 for the notations used):

$$\mathcal{Z}^k(T) := \Big\{ u^k : u^k_t \text{ is } \mathcal{A}_t\text{-measurable}, u^k \in L^2\Big(\Omega; B\big([0,T]; Z^k\big) \cap C^\mu_{\{0\}}\big([0,T]; Z^k\big)\Big)\Big\}. \tag{14}$$

Next, we need the following non-empty closed subsets of $\mathcal{Z}^k(T)$:

$$\begin{aligned} \mathcal{K}^1(T) := \Big\{ &u^1 \in \mathcal{Z}^1(T) : u^1(0) = u^1_0,\ \mathbb{E}(\|u^1\|^2_{B_Y})^{\frac{1}{2}} \le P_1, \\ &\mathbb{E}\Big[\Big(\sup_{\substack{t<s \\ t,s\in[0,T]}} \frac{\|u^1(t) - u^1(s)\|_Y}{|t-s|^{\frac{1}{2}+\mu}}\Big)^2\Big]^{\frac{1}{2}} \le P_2 \Big\}, \end{aligned} \tag{15}$$

$$\begin{aligned} \mathcal{K}^2(T) := \Big\{ &u^2 \in \mathcal{Z}^2(T) : \text{ for a.a. } \omega \in \Omega,\ u^2(0,\omega) = u^2_0(\omega), \\ &\|u^2(\omega)\|_{B_Z} \le P_1,\ \sup_{\substack{t<s \\ t,s\in[0,T]}} \frac{\|u^2(\omega,t) - u^2(\omega,s)\|_Z}{|t-s|^\mu} \le P_2 \Big\}, \end{aligned} \tag{16}$$

For $k \in \{3,4\}$ we define

$$\begin{aligned} \mathcal{K}^k(T) := \Big\{ &u^k \in \mathcal{Z}(T) : \text{ for a.a. } \omega \in \Omega,\ u^k(0,\omega) = u^k_0(\omega),\ \|u^k(\omega)\|_{B_Z} \le P_3, \\ &\|u^k(\omega)\|_{B_{Z_{\theta'}}} \le P_1,\ \sup_{\substack{t<s \\ t,s\in[0,T]}} \frac{\|u^k(\omega,t) - u^k(\omega,s)\|_{Z_{\theta'}}}{|t-s|^\mu} \le P_2 \Big\}. \end{aligned} \tag{17}$$

where P_1, P_2 and P_3 are some nonnegative constants and the constants μ, α, β, θ, and ν are such that

$$\left.\begin{array}{c} 0 < \mu' < \mu := 1 - \alpha', \quad \nu := 1 \\ 1 \ge \alpha > \alpha' > \theta > \theta' > \beta > \beta' > \frac{1}{2} \end{array}\right\} \tag{18}$$

These relationships will be assumed to hold throughout the whole Section 4.
Therefore, $0 < \mu' < \min(\beta, \mu) < \beta$. We also denote

$$\left.\begin{array}{l} \mathcal{Z}(T) := \mathcal{Z}^1(T) \times \mathcal{Z}^2(T) \times \mathcal{Z}^3(T) \times \mathcal{Z}^4(T), \\ \mathcal{K}(T) := \mathcal{K}^1(T) \times \mathcal{K}^2(T) \times \mathcal{K}^3(T) \times \mathcal{K}^4(T). \end{array}\right\} \tag{19}$$

4.1 Abstract Cauchy problem:

Now we formulate the equation system (2) in terms of an abstract Cauchy problem.

$$\begin{cases} \frac{d}{dt}\mathbf{u}(\omega,t) + \mathbb{A}(\mathbf{u}(\omega,t))\mathbf{u}(\omega,t) = \mathbf{r}(\mathbf{u}(\omega,t)), & \text{in } \mathbf{X},\ t > 0, \text{ for each } \omega \in \Omega. \\ \mathbf{u}(\omega,0) = \mathbf{u}_0(\omega), \end{cases} \tag{20}$$

where $\mathbf{X} := L^p(\mathfrak{D}) \times L^p(\mathfrak{D}) \times L^p(\mathfrak{D}) \times L^p(\mathfrak{D})$, $\mathbf{u} := (H_i, N, H_e, C)^T$, and

$$\mathbf{r}(\mathbf{u}(\omega,t)) = \begin{pmatrix} r^1(\mathbf{u}(\omega,t)) \\ r^2(\mathbf{u}(\omega,t)) \\ r^3(\mathbf{u}(\omega,t)) \\ r^4(\mathbf{u}(\omega,t)) \end{pmatrix} := \begin{pmatrix} J(u_t^4)\big(-T(u_t^1,u_t^3)+q_1-Q(u_t^1)\big) \\ 0 \\ J(u_t^4)\,T(u_t^1,\,u_t^3)+\nabla\cdot(h\nabla u_t^2) \\ u_t^4(1-u_t^4)\,\big(\Lambda_1(u_t^1,u_t^3)+\Lambda_2(u_t^1,u_t^3)\big)+q_3\,u_t^4-b\nabla u_t^3\cdot\nabla u_t^4 \end{pmatrix} \tag{21}$$

Next we collect some estimates for r^1 and for the vector $\mathbf{r}^{3,4} := (r^3, r^4)$.

Lemma 4.1. *Let the functions J, T, Q, Λ_1, Λ_2, f, and g satisfy the assumptions in Subsection 3.1. Then for each $\omega \in \Omega$, $r^1(\omega)$ maps $\mathcal{K}(T)$ into $C^\mu([0,T];Y)$, while $\mathbf{r}^{3,4}(\omega)$ maps $\mathcal{K}(T)$ into $C^\mu([0,T];\mathbf{X_B})$, where $\mathbf{X_B} := L^p(\mathfrak{D}) \times L^p(\mathfrak{D})$. This in turn yields that $\mathbf{r}$ maps $\mathcal{K}(T)$ into $F^{1,\mu}([0,T];\mathbf{X})$ (for this space see Definition 6).*

Proof. Since Y is a Banach algebra, if $\mathbf{v} \in \mathcal{K}(T)$ then by hypothesis we directly get that all the functions involved in r^1 are also in $B_Y := B([0,T];Y)$ (see Definition 4). Consequently,

$$\begin{aligned} &\|r_t^1\|_Y \le \|J(v_t^4)\|_Y\,\|T(v_t^1,v_t^3)\|_Y + q_1 + \|Q(v_t^1)\|_Y \\ \Rightarrow &\sup_{t\in[0,T]}\|r_t^1\|_Y \le \|J(v^4)\|_{B_Y}\,\|T(v^1,v^3)\|_{B_Y} + q_1 + \|Q(v^1)\|_{B_Y} \\ &\Rightarrow \|r^1\|_{B_Y} \le \mathrm{k}_{r^1}, \quad \mathrm{k}_{r^1} := \mathrm{k}_{suf}(\mathrm{M}_J(\mathrm{M}_T + q_1 + \mathrm{M}_Q)) < \infty, \end{aligned} \tag{22}$$

where $\mathrm{k}_{suf} < \infty$ is an sufficiently large constant.[3] However, in view of the nonlinearities in r^3 we have that

$$\begin{aligned} \|\mathbf{r}_t^{3,4}\|_{\mathbf{X_B}} &\le \|(\Lambda_1(v_t^1,v_t^3)+\Lambda_2(v_t^1,v_t^3))v_t^4(1-v_t^4)\|_{L^p(\mathfrak{D})} + q_3\|v_t^4\|_{L^p(\mathfrak{D})} + \|b\nabla v_t^3\cdot\nabla v_t^4\|_{L^p(\mathfrak{D})} \\ &\quad + \|J(v_t^4)T(v_t^1,v_t^3)+\tilde{q}_2 v_t^3\|_{L^p(\mathfrak{D})} + \|\nabla h\cdot\nabla v_t^2\|_{L^p(\mathfrak{D})} + \|h\Delta v_t^2\|_{L^p(\mathfrak{D})} \\ &\le \mathrm{M}_J\|T\|_{Z_{\theta'}} + (\mathrm{M}_{\Lambda_1}+\mathrm{M}_{\Lambda_2})\big(\|v_t^4\|_{Z_{\theta'}} + \|v_t^4\|^2_{Z_{\theta'}}\big) + \mathrm{M}_b\|v_t^3\|_{Z_{\theta'}}\|v_t^4\|_{Z_{\theta'}} \\ &\quad + q_3\|v_t^4\|_{Z_{\theta'}} + \|h\|_{Z_{\theta'}}\|v_t^2\|_{H_p^2(\mathfrak{D})} \\ \Rightarrow \sup_{t\in[0,T]}\|\mathbf{r}_t^{3,4}\|_{\mathbf{X_B}} &\le (\|v^4\|_{B_{Z_{\theta'}}} + \|v^4\|^2_{B_{Z_{\theta'}}})\|T\|_{B_{Z_{\theta'}}} + (\mathrm{M}_{\Lambda_1}+\mathrm{M}_{\Lambda_2})\big(\|v^4\|_{B_{Z_{\theta'}}} + \|v^4\|^2_{B_{Z_{\theta'}}}\big) \\ &\quad + \mathrm{M}_b\|v^3\|_{B_{Z_{\theta'}}}\|v^4\|_{B_{Z_{\theta'}}} + q_3\|v^4\|_{B_{Z_{\theta'}}} + \|h\|_{B_{Z_{\theta'}}}\|v^2\|_{B_Z} \\ \Rightarrow \|\mathbf{r}_t^{3,4}\|_{B_{\mathbf{X_B}}} &\le \mathrm{k}_{\mathbf{r}^{3,4}} < \infty, \\ \mathrm{k}_{\mathbf{r}^{3,4}} &:= \mathrm{k}_{suf}\Big((P_1+P_1^2)(\mathrm{k}_{\Lambda_1}+\mathrm{k}_{\Lambda_2}) + \mathrm{M}_J\mathrm{M}_T + \mathrm{M}_b P_1^2 + P_1(q_3+\mathrm{k}_h)\Big). \end{aligned} \tag{23}$$

Using (15) and Lemma 3.1 we can apply Kolmogorov-Čensov-Loève theorem to get the existence of μ-Hölder-continuous modification of the processes Λ_1, Λ_2 and J. Then due to the uniform boundedness of Λ_1, Λ_2 and J the Hölder semi-norms can be estimated (independent of ω) as

$$\sup_{\substack{t,s\in[0,T]\\ s<t}} \frac{\|\mathbf{r}_t^{3,4}-\mathbf{r}_s^{3,4}\|_{\mathbf{X_B}}}{|t-s|^\mu} \le \mathrm{k}_{L,\mathbf{r}^{3,4}} < \infty. \tag{24}$$

Similarly,

$$\sup_{\substack{t,s\in[0,T]\\ s<t}} \frac{\|r_t^1-r_s^1\|_Y}{|t-s|^\mu} \le \mathrm{k}_{L,r^1} < \infty, \tag{25}$$

where

$$\begin{aligned} &\mathrm{k}_{L,r^1} = 3\Big(\sup_{t\in[0,T]}\mathrm{k}_{L,r^1}(t)\Big)(P_1+P_2), \quad \mathrm{k}_{L,r^3} = \sup_{t\in[0,T]}\mathrm{k}_{L,r^3}(t), \quad \mathrm{k}_{L,r^4} = \sup_{t\in[0,T]}\mathrm{k}_{L,r^4}(t), \\ &\mathrm{k}_{L,\mathbf{r}^{3,4}} = 4(P_1+P_2)(\mathrm{k}_{L,r^3}+\mathrm{k}_{L,r^4}), \end{aligned}$$

with the constants depending on P_1, P_2, and the bounds of the coefficient functions involved in R_2 and R_3. ■

[3] The constant k_{suf} appears in a few more estimates below. In each case it represents an (arbitrarily chosen) sufficiently large positive real constant.

The proof of the following lemma is easily obtained from the assumptions about the coefficient functions made in Subsection 3.1.

Lemma 4.2. *Let the functions a, g, Λ_3, and Λ_4 be in $H^1_{2p}(\mathfrak{D})$. If $\mathbf{v} \in \mathcal{K}(T)$, then for each $\omega \in \Omega$, the operator $A_1(\omega)$ is in $C^{0,1}([0,T], \mathcal{L}(Y))$. Moreover, independently of ω, the operators A_2 and $\mathbf{B}$ belong to $C^{0,1}([0,T], \mathcal{L}(Y))$ and $C^{0,1}([0,T], \mathcal{L}(D(\mathbf{B}); \mathbf{X_B}))$, respectively.*

4.2 Evolution operator:

In order to solve the Cauchy problem 20, we first introduce (locally) its mild solution and then show that this is in fact the strong (local) solution. To this end we need to establish the corresponding evolution operator. The following lemmas achieve this goal.

Lemma 4.3. *As before, let*

$$\mathbf{X_B} := L^p(\mathfrak{D}) \times L^p(\mathfrak{D}),$$

and $\mathbf{v} \in \mathcal{K}(T)$. Then for each $\omega \in \Omega$, $U_\mathbf{B}(\omega, t, s)$ is a two parameter semigroup, called the evolution operator. It is an element of $\mathcal{L}(\mathbf{X_B})$ and it is defined like in Theorem 3.8 in [53]. Moreover, if $B_1(\omega, t)$, $B_2(\omega, t)$, and $B_3(\omega, t)$ are $\mathcal{A}_t$-measurable then $U_\mathbf{B}$ is $\mathcal{A}_t$-measurable.

Proof. For $\mathbf{v} \in \mathcal{K}(T)$ Theorem 3.6, Corollary 1, and Lemma 4.2 hold true. This in turn verifies the structural assumptions in Section 4.1. of [53] for $\nu = 1$. As a result Theorem 3.8 of [53] gives the required claim. As the operator $U_\mathbf{B}(t, s)$ is the limit of the evolution operator $U_{\mathbf{B}_n}(t, s)$ associated with the Yosida approximation $\mathbf{B}_n(t)$ of $\mathbf{B}(t)$, the $\mathcal{A}_t$-measurability claim holds due to $B_1(t)$, $B_2(t)$, and $B_3(t)$ being $\mathcal{A}_t$-measurable and the limits of these $\mathcal{A}_t$-measurable functions being again $\mathcal{A}_t$-measurable. ■

Lemma 4.4. *Let*

$$\mathbf{X_A} := H^1_{2p}(\mathfrak{D}) \times H^2_p(\mathfrak{D}),$$

and for each $\omega \in \Omega$, let $\mathbf{u}(\omega) \in \mathcal{K}$. Then $U_\mathbf{A}(\omega, t, s)$ defined as

$$U_\mathbf{A}(\omega, t, s) := \begin{bmatrix} U_{A_1}(t, s) & 0 \\ 0 & U_{A_2}(t, s) \end{bmatrix},$$

$$U_{A_1}(\omega, t, s) := \mathrm{e}^{-\int_s^t A_1(\omega, r)dr} = \mathrm{e}^{\int_s^t J(C(\omega,r))\xi(\omega,r)dr}, \tag{26}$$

$$U_{A_2}(\omega, t, s) := \mathrm{e}^{-\int_s^t A_2(\omega, r)dr} = \mathrm{e}^{-\int_s^t [\gamma_N C(\omega,r) - (\Lambda_3(\omega,r) - \Lambda_4(\omega,r))(1-N(\omega,r))]dr}. \tag{27}$$

is an element of $\mathcal{L}(\mathbf{X_A})$ and a uniformly continuous semigroup. Moreover, if $A_1(\omega, t)$ and $A_2(\omega, s)$ are $\mathcal{A}_t$-measurable then U_{A_1} and U_{A_2} are $\mathcal{A}_t$-measurable as well.

Proof. Since $\mathbf{v} \in \mathcal{K}$ implies that $u^4 \in L^\infty(\Omega; C([0, T]; Z^4))$, Lemma 3.3 and Lemma 3.2 imply that the operators $A_1(\omega)$ and $A_2(\omega)$ are bounded in the uniform topology and that they generate the respective claimed uniformly continuous semigroups. The $\mathcal{A}_t$-measurablility claim holds due to $A_1(t)$ and $A_2(t)$ being $\mathcal{A}_t$-measurable and the limits of measurable functions being still measurable. ■

Upon combining the above two lemmas we get the following theorem:

Theorem 4.5. *Let*

$$\mathbf{X} := \mathbf{X_A} \times \mathbf{X_B},$$

and for each $\omega \in \Omega$, let $\mathbf{v}(\omega) \in \mathcal{K}$. Then $U(\omega, t, s)$ defined as

$$U(\omega, t, s) := \begin{bmatrix} U_{A_1}(\omega, t, s) & 0 & \mathbf{0}^T \\ 0 & U_{A_2}(\omega, t, s) & \mathbf{0}^T \\ \mathbf{0} & \mathbf{0} & U_\mathbf{B}(\omega, t, s) \end{bmatrix}$$

is an element of $\mathcal{L}(\mathbf{X})$ and it forms a strongly continuous semigroup.

4.3 Approximate solution:

For $\mathbf{v} \in \mathcal{K}(T)$, $T > 0$ consider the following approximation of the Cauchy problem (20):

$$\begin{cases} \frac{d}{dt}\mathbf{u}(\omega,t) + \mathbb{A}(\mathbf{v}(\omega,t))\mathbf{u}(\omega,t) = \mathbf{r}(\mathbf{v}(\omega,t)), & \text{in } \mathbf{X},\ t \in (0,T], \text{ for each } \omega \in \Omega \\ \mathbf{u}(\omega,0) = u_0(\omega) \end{cases} \tag{28}$$

This is a non-autonomous inhomogeneous problem, which can be solved uniquely (for each fixed $\omega \in \Omega$) due to Theorem 7.5, and its mild solution is given by

$$\mathbf{u}(\omega,t) = U(\omega,t,0)\,\mathbf{u}_0 + \int_0^t U(\omega,t,s)\mathbf{r}(\mathbf{v}(\omega,s))ds, \tag{29}$$

with $U(\omega,t,s) := U(\omega,\mathbf{v}(t),\mathbf{v}(s))$ being the evolution operator for the operator $\mathbf{A}(\mathbf{v}(\omega,t))$ and $\mathbf{B}(\mathbf{v}(\omega,t))$, respectively. For the sake of clarity, we write out the mild solution componentwise:

$$u_t^1(\omega) := u^1(\omega,t) = U_{A_1}(\omega,t,0)u_0^1 + \int_0^t U_{A_1}(\omega,t,s)r_s^1(\mathbf{v}(\omega))ds \tag{30a}$$

$$u_t^2(\omega) := u^2(\omega,t) = U_{A_2}(\omega,t,0)u_0^2 \tag{30b}$$

$$\mathbf{u}_t^{3,4}(\omega) := \mathbf{u}^{3,4}(\omega,t) = U_{\mathbf{B}}(\omega,t,0)\mathbf{u}_0^{3,4} + \int_0^t U_{\mathbf{B}}(\omega,t,s)\mathbf{r}_s^{3,4}(\mathbf{v}(\omega))ds \tag{30c}$$

where,

$$r_s^1 = r^1(\mathbf{v}(\omega,s)) := J(v_s^4)\,\big(-T(v_s^1,v_s^3) + q_1 - Q(v_s^1)\big) \tag{31a}$$

$$\mathbf{r}_s^{3,4} = \begin{pmatrix} r^3(\mathbf{v}(\omega,s)) \\ r^4(\mathbf{v}(\omega,s)) \end{pmatrix} := \begin{pmatrix} J(v_s^4)\,T(v_s^1,\ v_s^3) + \tilde{q}_2 v_s^3 + \nabla\cdot(h\nabla v_s^2) \\ v_s^4(1-v_s^4)\,\big(\Lambda_1(v_s^1,v_s^3) + \Lambda_2(v_s^1,v_s^3)\big) + q_3 v_s^4 - b\nabla v^3\cdot\nabla v^4 \end{pmatrix}. \tag{31b}$$

Lemma 4.6. *Let $\mathbf{v} \in \mathcal{K}(T)$ and $\mathbf{u}_0^{3,4} := (u_0^3,u_0^4)^T \in D(\mathbf{B}_0^\alpha)$ be $\mathcal{A}_0$-measurable, $1 \geq \alpha > \theta$, $2\beta > 2\beta' := 1 + \frac{n}{2p}$ and $t \in [0,T]$. Then for each fixed $\omega \in \Omega$ and $\Xi \in \mathbb{R}_+^{12}$, the vector $\mathbf{u}_t^{3,4}(\omega) := (u_t^3(\omega),u_t^4(\omega))^T$ solves the abstract Cauchy problem*

$$\frac{d}{dt}\mathbf{u}_t^{3,4}(\omega) + \mathbf{B}(\mathbf{v}(\omega,t))\mathbf{u}_t^{3,4}(\omega) = \mathbf{r}^{3,4}(\mathbf{v}(\omega,t)), \quad \text{in } \mathbf{X_B}, \quad t > 0$$
$$\mathbf{u}^{3,4}(\omega,0) = \mathbf{u}_0^{3,4}(\omega).$$

Moreover, for each $\omega \in \Omega$ we have that

$$\mathbf{u}^{3,4} \in C([0,T];\mathbf{X_B}) \cap C^1((0,T];\mathbf{X_B}), \quad \mathbf{B}(\mathbf{v}_t)^\alpha\mathbf{u}^{3,4} \in C((0,T];\mathbf{X_B}), \tag{32}$$

with

$$\begin{cases} \|\mathbf{u}^{3,4}\|_{B_{\mathbf{X_B}}} + \|\mathbf{B}(\mathbf{v})^\alpha\mathbf{u}^{3,4}\|_{C_{\mathbf{X_B}}} \leq \mathrm{k}_{suf}\Big(\|\mathbf{B}_0^\alpha\mathbf{u}_0^{3,4}\|_{\mathbf{X_B}} + \|\mathbf{r}^{3,4}\|_{F^{\alpha,\mu'}}\Big) \\ \|\frac{d}{dt}\mathbf{u}^{3,4}\|_{F^{\alpha,\mu'}} + \|\mathbf{B}(\mathbf{v})\mathbf{u}^{3,4}\|_{F^{\alpha,\mu'}} \leq \mathrm{k}_{suf}\Big(\|\mathbf{B}_0^\alpha\mathbf{u}_0^{3,4}\|_{\mathbf{X_B}} + \|\mathbf{r}^{3,4}\|_{F^{\alpha,\mu'}}\Big) \end{cases} \tag{33}$$

Proof. For $\mathbf{v} \in \mathcal{K}(T)$ and $2\beta' := 1 + \frac{n}{2p}$, we see that the repulsion coefficient $g \in B([0,T];H_p^{2\beta'}(\mathfrak{D}))$ and the diffusion coefficient $a \in B([0,T];H_p^{2\beta'}(\mathfrak{D}))$ satisfy $\mathrm{m}_a \leq a \leq \mathrm{M}_a$. Therefore we can apply Theorem 3.6 and get that $\mathbf{B}(\mathbf{v}_t)$ is a sectorial operator with uniform spectral angle $\kappa_{\mathbf{B}} < \frac{\pi}{2}$ and its resolvent is satisfying the uniform upper bound (12). Moreover, $D(\mathbf{B}(\mathbf{v}_t)) = D(\mathbf{B}(\mathbf{v}_0))$ for all $t \in [0,T]$.
Since $\mathbf{u}_0^{3,4} \in D(\mathbf{B}_t^\alpha)$, for $t \in [0,T]$, the mapping $t \mapsto \mathbf{B}(\mathbf{v}_t)\mathbf{B}(\mathbf{v}_s)^{-1}$ is μ-Hölder continuous for any fixed $s \in [0,T]$ (due to the Lipschitz continuity of $\mathbf{B}$ proved in Lemma 4.2). Therefore, we can apply Theorem 7.5 with $\mathbf{r}^{3,4} \in C^\mu([0,T],\mathbf{X_B})$ (due to Lemma 4.1), thus $\mathbf{r}^{3,4} \in F^{\alpha,\mu'}([0,T];\mathbf{X_B})$, $\alpha > \theta > \beta$, $\mu > \mu'$ and $\nu = 1$, to get the required claim.
Finally, the solution process $\mathbf{u}_t^{3,4}$ is $\mathcal{A}_t$-measurable, since $\mathbf{u}_0^{3,4}$ is $\mathcal{A}_0$-measurable and integration of an $\mathcal{A}_t$-measurable function yields an $\mathcal{A}_t$-measurable function. ■

Lemma 4.7. *Let $\xi \in L^2(\Omega;C([0,\infty);\mathbb{R}))$ be a centered Gaussian process with μ-Hölder continuous covariance function, $\mathbf{v} \in \mathcal{K}(T)$, and $\mathbf{u}_0^{1,2} \in Z^1 \times Z^2$ be $\mathcal{A}_0$-measurable. Then for* *each $\omega \in \Omega$ and $\Xi \in \mathbb{R}_+^{12}$ the vector $\mathbf{u}_t^{1,2}(\omega) := (u_t^1(\omega), u_t^2(\omega))^T$ solves the abstract Cauchy problem*

$$\frac{d}{dt}\mathbf{u}_t^{1,2}(\omega) + \mathbf{A}(\mathbf{v}(\omega,t))\mathbf{u}_t^{1,2}(\omega) = \mathbf{r}^{1,2}(\mathbf{v}(\omega,t)), \quad \text{in } \mathbf{X}_\mathbf{A}, \quad t > 0$$
$$\mathbf{u}^{1,2}(\Omega, 0) = \mathbf{u}_0^{1,2}(\omega).$$

Moreover, for each $\omega \in \Omega$ we have that

$$\mathbf{u}^{1,2} \in C([0,T];\mathbf{X}_\mathbf{A}) \cap C^1((0,T];\mathbf{X}_\mathbf{A}), \quad \mathbf{A}(\mathbf{v})\mathbf{u}^{1,2} \in C([0,T];\mathbf{X}_\mathbf{A}), \tag{34}$$

with

$$\|\mathbf{u}^{1,2}\|_{B_{\mathbf{X}_\mathbf{A}}} + \|\frac{d}{dt}\mathbf{u}^{1,2}\|_{B_{\mathbf{X}_\mathbf{A}}} + \|\mathbf{A}(\mathbf{v})\mathbf{u}^{1,2}\|_{B_{\mathbf{X}_\mathbf{A}}} \le \mathrm{k}_{\xi,T}(\omega)(\|\mathbf{u}_0^{1,2}\|_{\mathbf{X}_\mathbf{A}} + \|\mathbf{r}^{1,2}(\mathbf{v})\|_{F^{\alpha,\mu'}}). \tag{35}$$

Proof. Since $v^3 \in L^\infty(\Omega; C^\mu([0,T]; Z_{\theta'}))$, from Lemma 3.2 and Lemma 3.3 we get that $\mathbf{A}(\omega,t) : H^1_{2p}(\mathfrak{D}) \times H^2_p(\mathfrak{D}) \to H^1_{2p}(\mathfrak{D}) \times H^2_p(\mathfrak{D})$, $p > n$ is a bounded linear operator which generates an uniformly continuous semigroup. This, along with the Lipschitz continuity of the reaction terms, yields the existence of a unique mild solution. The C^1 regularity of the mild solution in turn yields the existence of the strong solution. Finally, the solution process $\mathbf{u}_t^{1,2}$ is $\mathcal{A}_t$-measurable, since $\mathbf{u}_0^{1,2}$ is $\mathcal{A}_0$-measurable. The estimates for the claimed regularities can be obtained in a standard way; details are included in Step1.1 of the task validating the fact that the mapping defined in (36) below has a fixed point. ∎

4.4 Construction and properties of a fixed point mapping:

In the light of Lemmas 4.6 and 4.7, our next task is to show that the approximate solution (29) converges to the actual solution. To this aim we observe that the equation (29) can be seen as a mapping of a function $\mathbf{v}$ in $\mathcal{K}(T)$ into $\mathbf{u}$ (hopefully also in $\mathcal{K}(T)$). Therefore we define the mapping $\Phi(\mathbf{v}(t))$ as

$$\Phi(\mathbf{v}(\omega,t)) := \mathbf{u}(\omega,t) = U(\omega,t,0)\mathbf{u}_0(\omega) + \int_0^t U(\omega,t,s)\mathbf{r}(\mathbf{v}(\omega,s))ds \tag{36}$$

Now the aim is to show that $\Phi : \mathcal{K}(T) \to \mathcal{K}(T)$ is a fixed point mapping in $\mathcal{Z}$.

4.4.1 Step1: Φ maps $\mathcal{K}(T)$ into $\mathcal{K}(T)$:

Since Φ is a vector mapping with $\Phi = (\Phi_1,\ \Phi_2,\ \Phi_3,\ \Phi_4)^T$, we prove the claim componentwise, i.e. for each Φ_k, $k \in \{1,\ 2,\ 3,\ 4\}$.

1.1 Verification of $u^1(\omega) \in \mathcal{K}(T)$: In order to prove the regularity properties of u^1 we need to assume that the process $(\xi_t)_t$ has independent increments and either u_0^1 is deterministic or the σ- algebra generated by u_0^1 is independent of $\mathcal{A}_s$.

1.1.a Boundedness:

$$\begin{aligned}
u_t^1(\omega) = \Phi_1(\mathbf{v}(\omega,t)) &:= U_{A_1}(\omega,t,0)u_0^1(\omega) + \int_0^t U_{A_1}(\omega,t,s)r_s^1(\mathbf{v}(\omega))ds \\
&= \mathrm{e}^{\int_0^t J(v_r^4(\omega))\xi_r(\omega)dr}u_0^1(\omega) + \int_0^t \mathrm{e}^{\int_s^t J(v_r^4(\omega))\xi_r(\omega)dr}r^1(\mathbf{v}(\omega,s))ds \\
\Rightarrow \|u_t^1(\omega)\|_Y &\le \|\mathrm{e}^{\int_0^t \cdot}\|_Y\|u_0^1(\omega)\|_Y + \int_0^t \|\mathrm{e}^{\int_s^t \cdot}\|_Y\|r^1(\mathbf{v}(\omega,s))\|_Y ds \\
\Rightarrow \|u_1(\omega)\|_{B_Y} &\le \|\mathrm{e}^{\int_0^t \cdot}\|_{B_Y}\|u_0^1(\omega)\|_Y + \|r^1(\mathbf{v}(\omega))\|_{B_Y}\|\mathrm{e}^{\int_0^t \cdot}\|_{B_Y}T
\end{aligned} \tag{37}$$

$$\begin{aligned}
\Rightarrow \mathbb{E}[\|u_1(\omega)\|_{B_Y}^2] &\le \mathbb{E}[\|\mathrm{e}^{\int_0^t \cdot}\|_{B_Y}^2]\Big(\mathbb{E}\|u_0^1\|_Y + \|r^1(\mathbf{v}(\omega))\|_{B_Y}T\Big)^2 \\
&\overset{(78)}{\le} \mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}_{\xi_T}^2}\Big(\mathbb{E}\|u_0^1\|_Y + \|r^1(\mathbf{v}(\omega))\|_{B_Y}T\Big)^2.
\end{aligned} \tag{38}$$

Thus $u^1 \in L^2\Big(\Omega; B\big([0,T];Y\big)\Big)$ and $\mathbb{E}[\|u^1\|_{B_Y}^2]^{\frac{1}{2}} \le P_1$ for $T > 0$ small enough.

1.1.b Hölder continuity:

$$
\begin{aligned}
u^1_t - u^1_s = \Phi_1(\mathbf{v}_t) - \Phi_1(\mathbf{v}_s) &= [U_{A_1}(t,s) - 1]u^1_s + \int_s^t U_{A_1}(t,\tau) r^1_\tau(\mathbf{v}) d\tau \\
&= [\mathrm{e}^{\int_s^t A_1(\tau)d\tau} - 1]u^1_s + \int_s^t \mathrm{e}^{\int_\tau^t A_1(\rho)d\rho} r^1_\tau(\mathbf{v}) d\tau \\
\Rightarrow \|u^1_t - u^1_s\|_Y \le & \left\| [\mathrm{e}^{\int_s^t A_1(\tau)d\tau} - 1] \right\|_Y \|u^1_s\|_Y \\
& + \sup_{\tau \in [0,T]} \Big(\Big(\sup_{r \in [\tau,T]} \left\| \mathrm{e}^{\int_r^T A_1(\rho)d\rho} \right\|_Y \Big) \Big(\sup_{r \in (0,\tau]} \|r^1_r(\mathbf{v})\|_Y \Big) \Big) \int_s^t d\tau.
\end{aligned}
$$

By using (88) and $r^1 \in L^\infty(\Omega; B_Y)$, we get that

$$
\begin{aligned}
\mathbb{E}\Big[\Big(\sup_{\substack{t,s \in [0,T] \\ s<t}} \frac{\|u^1_t - u^1_s\|_Y}{|t-s|^{\frac{1}{2}+\mu}} \Big)^2\Big] &\le T^{1-2\mu}\, \mathbb{E}\Big[\Big(\sup_{\substack{t,s \in [0,T] \\ s<t}} \frac{\|\mathrm{e}^{\int_s^t A_1(\tau)d\tau} - 1\|^2_Y}{|t-s|} \Big)^2 \|u^1_s\|^2_{B_Y}\Big] \\
&\quad + T^{1-2\mu}\, \mathbb{E}\Big[\left\| \mathrm{e}^{\int_0^\tau A_1(\rho)d\rho} \right\|^2_{B_Y} \Big] \mathbb{E}\Big[\|r^1(\mathbf{v})\|^2_{B_Y} \Big] \\
&\overset{(79),(78),(88)}{\le} T^{1-2\mu} \mathrm{k}_{suf} \mathrm{e}^{\mathrm{k}_{suf} \mathrm{k}^2_{2,\xi_{T_1}}} \Big(\mathbb{E}[\|u_0\|^2_Y] + \mathbb{E}[\|u_s\|^2_{B_Y}] + \mathbb{E}[\|r^1\|^2_{B_Y}] \Big) \\
&\le T^{1-2\mu} \mathrm{k}_{suf} \mathrm{e}^{\mathrm{k}_{suf} \mathrm{k}^2_{2,\xi_{T_1}}} \Big(2P_1^2 + \mathrm{k}^2_{r_1} \Big). \qquad (39)
\end{aligned}
$$

Therefore, $u^1 \in L^2\Big(\Omega; C^\mu([0,T];Y)\Big)$ with $\mathbb{E}\Big[\Big(\sup_{\substack{t<s \\ t,s \in [0,T]}} \frac{\|u^1(t) - u^1(s)\|_Y}{|t-s|^{\frac{1}{2}+\mu}} \Big)^2\Big]^{\frac{1}{2}} \le P_2$ for $T > 0$ small enough.

1.1.c Boundedness in $F^{\beta,\mu}$: Let $\omega \in \Omega$ be fixed, then

$$
A_1(\omega,t)u^1_t(\omega) = -J(v^4_t)\xi_t u^1_t.
$$

Using (83) we immediately have that

$$
\mathbb{E}[\|A_1 u^1_t\|^2_{B_Y}] \le \mathrm{M}^2_J \mathrm{k}^2_{\xi_{2,T}}\, \mathrm{e}^{4\mathrm{k}^2_{\xi_{2,T}}}.
$$

Due to Lemma 4.2 (in particular the Lipschitz continuity of A_1) and due to the Hölder continuity of u^4_t and ξ_t (a.s.) we get that $A_1(t)u^1(t)$ is Hölder continuous, as a result of which

$$
\begin{aligned}
\|A_1(\omega,t)u^1_t - A_1(\omega,s)u^1_s\|_Y &\le \|A_1(\omega,t) - A_1(\omega,s)\|_Y \|u^1_s\|_Y + \|A_1(\omega,t)\|_Y \|u^1_t(\omega) - u^1_s(\omega)\|_Y \\
&\le |\xi_s(\omega)| \mathrm{M}_{J'} \|v^4(\omega,t) - v^4(\omega,s)\|_Y + \mathrm{M}_J |\xi_t - \xi_s| \|u^1_t\|_Y \\
&\quad + \mathrm{M}_J |\xi_t| \|u^1_t(\omega) - u^1_s(\omega)\|_Y.
\end{aligned}
$$

Due to (83), (84), (39) and to the μ-Hölder continuity of the covariance function of ξ_t, we get that

$$
\mathbb{E}\Big[\Big(\sup_{t,s \in [0,T]} \frac{\|A_1(\omega,t)\|_Y \|u^1_t(\omega) - u^1_s(\omega)\|_Y}{|t-s|^\mu} \Big)^2\Big] \le \mathrm{k}_{suf} < \infty.
$$

Thus, we have $A_1 u^1_t \in L^2\Big(\Omega; C^\mu([0,T];Y)\Big)$. This immediately ensures that $A_1 u^1 \in L^2\Big(\Omega; F^{\beta,\mu}([0,T];Y)\Big)$ for $\beta' \in [0,1]$ with $\beta' > \mu > 0$.

1.1.d C^1 continuity: Let $\omega \in \Omega$ be fixed, then

$$
\begin{aligned}
u^1_{t+h} - u^1_t &= [\mathrm{e}^{\int_t^{t+h} A_1(s)ds} - 1]u^1_t + \int_t^{t+h} \mathrm{e}^{\int_s^{t+h} A_1(\tau)d\tau} r^1_s(\mathbf{v}) ds \\
\Rightarrow \frac{1}{h}[u^1_{t+h} - u^1_t] &= \frac{1}{h}\Big[\sum_{k=2}^\infty \frac{\big(\int_t^{t+h} A_1(s)ds\big)^k}{k!} \Big] u^1_t + \frac{1}{h}\int_t^{t+h} A_1(s)u^1_t ds \\
&\quad + \frac{1}{h}\int_t^{t+h} \mathrm{e}^{\int_s^{t+h} A_1(\tau)d\tau} r^1_s(\mathbf{v}) ds.
\end{aligned}
$$

Due to the a.s. continuity of v_t^4 in Y and the uniform continuity (for a.e. $\omega \in \Omega$) of the semigroup $U_{A_1}(t,s)$ in Y with respect to both t and s, by taking the limit $h \to 0$ we get

$$\frac{d}{dt}u^1(\omega,t) = A_1(\omega,t)u_t^1(\omega) + r_t^1((\mathbf{v}(\omega)).$$

Due to the continuity of $A_1(t)u_t^1$ and $r^1(\mathbf{v}_t)$ in Y, we get that for a.e. $\omega \in \Omega$, $u^1(\omega) \in C^1((0,T];Y)$.

1.2 Verification of $u^2(\omega) \in \mathcal{K}(T)$: Analogously to $u^1(\omega) \in \mathcal{K}(T)$.

1.3 Verification of $\mathbf{u}^{3,4}(\omega) \in \mathcal{K}(T)$:

1.3.a Boundedness: For each $\omega \in \Omega$ we have

$$\begin{aligned}
\begin{pmatrix} u^3(t) \\ u^4(t) \end{pmatrix} &:= \begin{pmatrix} \Phi_3(\mathbf{v}(t)) \\ \Phi_4(\mathbf{v}(t)) \end{pmatrix} = U_{\mathbf{B}}(\omega,t,0)\begin{pmatrix} u_{3,0} \\ u_{4,0} \end{pmatrix} + \int_0^t U_{\mathbf{B}}(t,s)\begin{pmatrix} r^3(\mathbf{v}(s)) \\ r^4(\mathbf{v}(s)) \end{pmatrix} ds \\
&= \mathbf{u}_0^{3,4} + (\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1)\mathbf{u}_0^{3,4} + (U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))})\mathbf{u}_0^{3,4} \\
&+ \int_0^t U_{\mathbf{B}}(t,s)[\mathbf{r}^{3,4}(\mathbf{v}(s)) - \mathbf{r}^{3,4}(\mathbf{v}(t))]ds + \int_0^t [U_{\mathbf{B}}(t,s) - \mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))}]\mathbf{r}^{3,4}(\mathbf{v}(t))ds \\
&+ \int_0^t [\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))} - \mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_0)}]\mathbf{r}^{3,4}(\mathbf{v}(t))ds + [\mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))} - 1]\mathbf{B}_0^{-1}\mathbf{r}^{3,4}(\mathbf{v}(t))
\end{aligned}$$

$$\begin{aligned}
\Rightarrow \|\mathbf{u}^{3,4}(t)\|_{\mathbf{Z}_{\theta'}^{3,4}} &\le \|u_0^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}} + \|(\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1)\mathbf{u}_0^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}} + \|(U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))})\mathbf{u}_0^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}} \\
&+ \left\| \int_0^t U_{\mathbf{B}}(t,s)[\mathbf{r}^{3,4}(\mathbf{v}(s)) - \mathbf{r}^{3,4}(\mathbf{v}(t))]ds \right\|_Z + \left\| \int_0^t [U_{\mathbf{B}}(t,s) - \mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))}]\mathbf{r}^{3,4}(\mathbf{v}(t))ds \right\|_{\mathbf{Z}_{\theta'}^{3,4}} \\
&+ \left\| \int_0^t [\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))} - \mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_0)}]\mathbf{r}^{3,4}(\mathbf{v}(t))ds \right\|_{\mathbf{Z}_{\theta'}^{3,4}} + \left\| [\mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))} - 1]\mathbf{B}_0^{-1}\mathbf{r}^{3,4}(\mathbf{v}(t)) \right\|_{\mathbf{Z}_{\theta'}^{3,4}}
\end{aligned}$$

Now let us estimate each term on the right hand side.

Term2:

$$\begin{aligned}
\left\|(\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1)\mathbf{u}_0^{3,4}\right\|_{\mathbf{Z}_{\theta'}^{3,4}} &\le \mathrm{k}_{\theta,\theta'}\left\|\mathbf{B}(\mathbf{u}_0)^{\theta}[\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1]\mathbf{u}_0^{3,4}\right\|_{\mathbf{X}_{\mathbf{B}}} \\
&\le \mathrm{k}_{\theta,\theta'}\left\|[\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1]\mathbf{B}(\mathbf{u}_0)^{\theta-\alpha}\right\|_{\mathcal{L}(\mathbf{X}_{\mathbf{B}})}\|\mathbf{B}(\mathbf{u}_0)^{\alpha}\mathbf{u}_0^{3,4}\|_{\mathbf{X}_{\mathbf{B}}} \\
&\overset{[53,(2.129)]}{\le} \mathrm{k}_{\theta,\theta'}\mathrm{k}_{\mathbf{B}_{0,\theta}}\, t^{\alpha-\theta}\|\mathbf{B}(\mathbf{u}_0)^{\alpha}\mathbf{u}_0^{3,4}\|_{\mathbf{X}_{\mathbf{B}}}
\end{aligned}$$

$$\Rightarrow \left\|(\mathrm{e}^{-t(\mathbf{B}(\mathbf{u}_0))} - 1)\mathbf{u}_0^{3,4}\right\|_{B_{\mathbf{Z}_{\theta'}^{3,4}}} \le \mathrm{k}_{\theta,\theta'}\mathrm{k}_{\mathbf{B}_{0,\theta}}\, T^{\alpha-\theta}\|\mathbf{B}(\mathbf{u}_0)^{\alpha}\mathbf{u}_0^{3,4}\|_{\mathbf{X}_{\mathbf{B}}}.$$

Term3:

$$\begin{aligned}
\left\|U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))})\mathbf{u}_0^{3,4}(\omega)\right\|_{\mathbf{Z}_{\theta'}^{3,4}} &\le \mathrm{k}_{\theta,\theta'}\left\|\mathbf{B}(\mathbf{v}_0)^{\theta}[U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))}]\mathbf{u}_0^{3,4}\right\|_{\mathbf{X}_{\mathbf{B}}} \\
&= \mathrm{k}_{\theta,\theta'}\left\|\mathbf{B}(\mathbf{v}_0)^{\theta}[U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))}]\mathbf{B}(\mathbf{v}_0)^{-\alpha}\right\|_{\mathcal{L}(\mathbf{X}_{\mathbf{B}})}\left\|\mathbf{B}(\mathbf{v}_0)^{\alpha}\mathbf{u}_0^{3,4}(\omega)\right\|_{\mathbf{X}_{\mathbf{B}}} \\
&\overset{[53,(3.87)]}{\le} \mathrm{k}_{\theta,\theta'}\,\mathrm{k}_{\mathbf{B}_{0,\theta,\alpha}}\, t^{\alpha-\theta+\mu+\nu-1}\left\|\mathbf{B}(\mathbf{v}_0)^{\alpha}\mathbf{u}_0^{3,4}(\omega)\right\|_{\mathbf{X}_{\mathbf{B}}}
\end{aligned}$$

$$\Rightarrow \left\|U_{\mathbf{B}}(t,0) - \mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))})\mathbf{u}_0^{3,4}\right\|_{B_{\mathbf{Z}_{\theta'}^{3,4}}} \le \mathrm{k}_{\theta,\theta'}\,\mathrm{k}_{\mathbf{B}_{0,\theta}}\, T^{\alpha-\theta+\mu+\nu-1}\left\|\mathbf{B}(\mathbf{v}_0)^{\alpha}\mathbf{u}_0^{3,4}(\omega)\right\|_{\mathbf{X}_{\mathbf{B}}}.$$

Term4:

$$\left\|\int_0^t U_{\mathbf{B}}(t,s)[\mathbf{r}^{3,4}(s)-\mathbf{r}^{3,4}(t)]ds\right\|_{\mathbf{Z}^{3,4}_{\theta'}} \leq \mathrm{k}_{\theta,\theta'}\int_0^t \left\|\mathbf{B}(\mathbf{v}_t)^\theta U_{\mathbf{B}}(t,s)\right\|_{\mathcal{L}(\mathbf{X_B})}\left\|[\mathbf{r}^{3,4}(s)-\mathbf{r}^{3,4}(t)]\right\|_{\mathbf{X_B}}ds$$

$$\overset{[53,(3.81)]}{\leq} \mathrm{k}_{\theta,\theta'}\int_0^t (t-s)^{-\theta}(t-s)^{\mu}\left\|(t-s)^{-\mu}[\mathbf{r}^{3,4}(s)-\mathbf{r}^{3,4}(t)]\right\|_{\mathbf{X_B}}ds$$

$$\leq \mathrm{k}_{\theta,\theta'}\int_0^t \mathrm{k}_{\mathbf{B}_t,\theta}(t-s)^{\mu-\theta}\sup_{\substack{s<t,\\ t,s\in[0,T]}}\left\|(t-s)^{-\mu}[\mathbf{r}^{3,4}(s)-\mathbf{r}^{3,4}(t)]\right\|_{\mathbf{X_B}}ds$$

$$\leq \mathrm{k}_{\theta,\theta'}\mathrm{k}_{\mathbf{B}_t,\theta}\mathrm{k}_{\mathbf{r}^{3,4}}\int_0^t (t-s)^{\mu-\theta}ds$$

$$\Rightarrow \left\|\int_0^t U_{\mathbf{B}}(t,s)[\mathbf{r}^{3,4}(s)-\mathbf{r}^{3,4}(t)]ds\right\|_{B_{\mathbf{Z}^{3,4}_{\theta'}}} \leq \frac{\mathrm{k}_{\theta,\theta'}\mathrm{k}_{\mathbf{B}_t,\theta}\mathrm{k}_{\mathbf{r}^{3,4}}}{\mu-\theta+1}\,T^{\mu-\theta+1}.$$

Term5:

$$\left\|\int_0^t [U_{\mathbf{B}}(t,s)-\mathrm{e}^{-(t-s)\mathbf{B}(\mathbf{v}_s)}]\mathbf{r}^{3,4}_t ds\right\|_{\mathbf{Z}^{3,4}_{\theta'}} \leq \int_0^t \mathrm{k}_{\theta,\theta'}\left\|\mathbf{B}(\mathbf{v}_t)^\theta[U_{\mathbf{v}}(t,s)-\mathrm{e}^{-(t-s)\mathbf{B}(\mathbf{v}_s)}]\right\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{r}^{3,4}_t\|_{\mathbf{X_B}}ds$$

$$\overset{[53,(3.87)]}{\leq} \mathrm{k}_{\theta,\theta'}\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}\int_0^t \mathrm{k}_{\mathbf{B}_t,\theta}(t-s)^{\mu+\nu-1-\theta}ds$$

$$\leq \frac{\mathrm{k}_{\mathbf{B}_t,\theta}\mathrm{k}_{\theta,\theta'}}{\mu+\nu-\theta}\,t^{\mu+\nu-\theta}\,\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}\quad(\text{since }\mu+\nu-\theta-1>-1)$$

$$\Rightarrow \left\|\int_0^t [U_{\mathbf{B}}(t,s)-\mathrm{e}^{-(t-s)\mathbf{B}(\mathbf{v}_s)}]\mathbf{r}^{3,4}_t ds\right\|_{B_{\mathbf{Z}^{3,4}_{\theta'}}} \leq \frac{\mathrm{k}_{\mathbf{B}_t,\theta}\mathrm{k}_{\theta,\theta'}}{\mu+\nu-\theta}\,T^{\mu+\nu-\theta}\,\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}.$$

Term6:

$$\left\|\int_0^t [\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))}-\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_0)}]\mathbf{r}^{3,4}_t ds\right\|_{\mathbf{Z}^{3,4}_{\theta'}} \leq \int_0^t \mathrm{k}_{\theta,\theta'}\left\|\mathbf{B}(\mathbf{v}_t)^\theta[U_{\mathbf{B}}(t,s)-\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))}]\right\|_{\mathcal{L}L^p(\mathfrak{D})}\|\mathbf{r}^{3,4}_t\|_{\mathbf{X_B}}ds$$

$$\overset{[53,(3.91)]}{\leq} \mathrm{k}_{\theta,\theta'}\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}\int_0^t \mathrm{k}_{\mathbf{B}_t,\theta}(t-s)^{\mu+\nu-1-\theta}ds$$

$$\Rightarrow \left\|\int_0^t [\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_s))}-\mathrm{e}^{-(t-s)(\mathbf{B}(\mathbf{v}_0)}]\mathbf{r}^{3,4}_t ds\right\|_{\mathbf{Z}^{3,4}_{\theta'}} \leq \frac{\mathrm{k}_{\theta,\theta'}\,\mathrm{k}_{\mathbf{B}_t,\theta}}{\mu+\nu-\theta}\,T^{\mu+\nu-\theta}\,\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}.$$

Term7:

$$\left\|[\mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))}-1]\mathbf{B}_0^{-1}\mathbf{r}^{3,4}_t\right\|_{\mathbf{Z}^{3,4}_{\theta'}} \leq \mathrm{k}_{\theta,\theta'}\left\|[\mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))}-1]\mathbf{B}(\mathbf{v}_0)^{\theta-1}\right\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{r}^{3,4}_t\|_{\mathbf{X_B}}$$

$$\Rightarrow \left\|[\mathrm{e}^{-t(\mathbf{B}(\mathbf{v}_0))}-1]\mathbf{B}_0^{-1}\mathbf{r}^{3,4}_t\right\|_{B_{\mathbf{Z}^{3,4}_{\theta'}}} \leq \mathrm{k}_{\theta,\theta'}\mathrm{k}_{\mathbf{B}_0,\theta}\,T^{1-\theta}\,\|\mathbf{r}^{3,4}\|_{B_{\mathbf{X_B}}}.$$

Altogether, we get that $\|\mathbf{u}^{3,4}\|_{B_{\mathbf{Z}^{3,4}_{\theta'}}} \leq P_1$ for $T>0$ sufficiently small.
Moreover, due to the estimate (33) and by setting

$$\Big(\|\mathbf{B}_0^\alpha\mathbf{u}_0^{3,4}\|_{\mathbf{X_B}}+\|\mathbf{r}^{3,4}(\mathbf{v})\|_{F^{\alpha,\mu'}}\Big) \leq \mathrm{k}_{suf}\Big(\|\mathbf{B}_0^\alpha\mathbf{u}_0^{3,4}\|_{\mathbf{X_B}}+\|\mathbf{r}^{3,4}(\mathbf{v})\|_{F^{\alpha,\mu}}\Big) \leq P_3<\infty$$

we also get that $\|\mathbf{u}^{3,4}\|_{B_Z} \leq P_3$.

1.3.b Hölder continuity:

$$\mathbf{u}^{3,4}_t-\mathbf{u}^{3,4}_s = \Phi^{3,4}(\mathbf{v}_t)-\Phi^{3,4}(\mathbf{v}_t) = [U_{\mathbf{B}}(\omega,\mathbf{v}_t,\mathbf{v}_s)-1]\mathbf{u}^{3,4}_s+\int_s^t U_{\mathbf{B}}(\omega,\mathbf{v}_t,\mathbf{v}_\tau)\mathbf{r}^{3,4}_\tau(\mathbf{v})d\tau$$

$$\|\mathbf{u}_t^{3,4}-\mathbf{u}_s^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}} \le \left\|[U_{\mathbf{B}}(t,s)-\mathrm{e}^{-(t-s)\mathbf{B}(\mathbf{v}_s)}]\mathbf{B}(\mathbf{v}_s)^{-1}\mathbf{B}(\mathbf{v}_s)^1\mathbf{u}_s^{3,4}\right\|_{\mathbf{Z}_{\theta'}^{3,4}}$$
$$+\left\|[\mathrm{e}^{-(t-s)\mathbf{B}(\mathbf{v}_s)}-1]\mathbf{B}(\mathbf{v}_s)^{-1}\mathbf{B}(\mathbf{v}_s)^1\mathbf{u}_s^{3,4}\right\|_{\mathbf{Z}_{\theta'}^{3,4}}+\int_t^s\left\|U_{\mathbf{B}}(t,\tau)\mathbf{r}_\tau^{3,4}(\mathbf{v})\right\|_{\mathbf{Z}_{\theta'}^{3,4}}d\tau.$$

Estimating each term on the right hand side similarly as above we obtain

$$\sup_{t,s\in[0,T]}\frac{\|\mathbf{u}_t^{3,4}-\mathbf{u}_s^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}}}{|t-s|^\mu}\le \mathrm{k}_{suf}T^\epsilon(\|\mathbf{u}^{3,4}\|_{B_{\mathbf{Z}_{\theta'}^{3,4}}}+\|\mathbf{r}^{3,4}(\mathbf{v})\|_{B_{\mathbf{X_B}}}),$$

from which it follows that

$$\sup_{t,s\in[0,T]}\frac{\|\mathbf{u}_t^{3,4}-\mathbf{u}_s^{3,4}\|_{\mathbf{Z}_{\theta'}^{3,4}}}{|t-s|^\mu}\le P_2$$

for $T>0$ sufficiently small.

4.4.2 Step2: Φ is a contraction in $\mathcal{Z}(T)$:

Let $\mathbf{v}^1$ and $\mathbf{v}^2$ be in $\mathcal{K}(T)$. Then $\Psi(\mathbf{v}_t^k):\mathcal{K}(T)\to\mathcal{K}(T)$, where

$$\Psi_t^k:=\Psi(\mathbf{v}_t^k)=\begin{pmatrix}\Phi_3(\mathbf{v}_t^k)\\ \Phi_4(\mathbf{v}_t^k)\end{pmatrix}\quad\text{and}\quad \mathbf{f}_t^k:=\mathbf{f}(\mathbf{v}_t^k)=\begin{pmatrix}r^3(\mathbf{v}_t^k)\\ r^4(\mathbf{v}_t^k)\end{pmatrix}.$$

$$\Psi_t^1-\Psi_t^2=\big(U_{\mathbf{B}}^1(t,0)-U_{\mathbf{B}}^2(t,0)\big)\mathbf{u}_0^{3,4}+\int_0^t\big(U_{\mathbf{B}}^1(t,s)-U_{\mathbf{B}}^2(t,s)\big)\mathbf{f}_s^1ds+\int_0^tU_{\mathbf{B}}^2(t,s)\big(\mathbf{f}_s^1-\mathbf{f}_s^2\big)ds.$$

Let $\mathbf{u}_0^{3,4}\in D(\mathbf{B}_0^\alpha)$, with $1\ge\alpha>\beta>0$. Now taking the $\mathbf{Z}_{\beta'}^{3,4}$-norm and using the embedding $D(\mathbf{B}_t^\beta)\hookrightarrow\mathbf{Z}_{\beta'}^{3,4}$ under the conditions (18), we get with the notation $\mathbf{B}_1(t)^\beta:=\mathbf{B}(\mathbf{v}^1(t))^\beta$:

$$\begin{aligned}\|\mathbf{B}_1^\beta(t)[\Psi_t^1-\Psi_t^2]\|_{\mathbf{X_B}}&\le\|\mathbf{B}_1^\beta(t)[\big(U_{\mathbf{B}}^1(t,0)-U_{\mathbf{B}}^2(t,0)\big)\mathbf{u}_0^{3,4}]\|_{\mathbf{X_B}}+\int_0^t\|\mathbf{B}_1^\beta(t)[\big(U_{\mathbf{B}}^1(t,s)-U_{\mathbf{B}}^2(t,s)\big)\mathbf{f}_s^1]\|_{\mathbf{X_B}}ds\\&\quad+\int_0^t\|\mathbf{B}_1^\beta(t)[U_{\mathbf{B}}^2(t,s)\big(\mathbf{f}_s^1-\mathbf{f}_s^2\big)]\|_{\mathbf{X_B}}ds\\&=\text{ Term1}+\text{ Term2}+\text{ Term3}\end{aligned}$$

Term1: Firstly, using the Yosida approximation $\mathbf{B}_n(t)$ of $\mathbf{B}(t)$ and its associated evolution operator $U_{\mathbf{B}_n}(t)$, we have that (for the properties of $U_{\mathbf{B}_n}$ see Section 5 in Chapter 3, [53])

$$\begin{aligned}U_{\mathbf{B}_n}^1(t,0)-U_{\mathbf{B}_n}^2(t,0)&=-\int_0^t\frac{d}{ds}U_{\mathbf{B}_n}^1(t,s)U_{\mathbf{B}_n}^2(s,0)ds\\&=\int_0^tU_{\mathbf{B}_n}^1(t,s)\mathbf{B}_{2,n}(s)U_{\mathbf{B}_n}^2(s,0)-U_{\mathbf{B}_n}^1(t,s)\mathbf{B}_{1,n}(s)U_{\mathbf{B}_n}^2(s,0)ds\\&=\int_0^tU_{\mathbf{B}_n}^1(t,s)\mathbf{B}_{1,n}^{1-\nu}(s)\mathbf{B}_{1,n}^\nu(s)[\mathbf{B}_{1,n}^{-1}(s)-\mathbf{B}_{2,n}^{-1}(s)]\mathbf{B}_{2,n}(s)U_{\mathbf{B}_n}^2(s,0)ds.\end{aligned}$$

Therefore,

$$\begin{aligned}\mathbf{B}_{1,n}^\beta(t)\big(U_{\mathbf{B}_n}^1(t,0)-U_{\mathbf{B}_n}^2(t,0)\big)\mathbf{B}_{2,n}^{-\alpha}(0)&=\int_0^t\mathbf{B}_{1,n}^\beta(t)U_{\mathbf{B}_n}^1(t,s)\mathbf{B}_{1,n}^{1-\nu}(s)\mathbf{B}_{1,n}^\nu(s)[\mathbf{B}_{1,n}^{-1}(s)-\mathbf{B}_{2,n}^{-1}(s)]\\&\quad\times\mathbf{B}_{2,n}(s)U_{\mathbf{B}_n}^2(s,0)\mathbf{B}_{2,n}^{-\alpha}(0)ds.\end{aligned}\tag{40}$$

Now due to the following properties:

1. $(t,s)\mapsto U_n(t,s)$ is continuous in the uniform topology $\forall s,t\in[0,T]$, $s\le t$.
2. $U_n(t,s)\to U(t,s)$ strongly in $\mathbf{X_B}$, with $s<t,s,t\in[0,T]$.
3. $t\mapsto U(t,s)$ is continuous in the strong topology for $t\in[s,T]$, $s\in[0,T)$. Similarly, $s\mapsto U(t,s)$ is continuous in the strong topology for $s\in[0,t]$, $t\in(0,T]$.
4. The mapping $s\mapsto\mathbf{B}_{1,n}^\beta U_{\mathbf{B}_n}^1(t,s)$, for fixed $t\in(s,T]$ is continuous in the uniform topology with $\left\|\mathbf{B}_{1,n}^\beta U_{\mathbf{B}_n}^1(t,s)\right\|_{\mathbf{X_B}}\le\mathrm{k}_{suf}|t-s|^{-\beta}$. Moreover, $s\mapsto(t-s)^{-\beta}\in L^1([0,t])$. Finally, $\mathbf{B}_{1,n}^\beta U_{\mathbf{B}_n}^1(t,s)\overset{n\to\infty}{\to}\mathbf{B}_1^\beta U_{\mathbf{B}}^1(t,s)$ in the strong topology.

5. The mapping $s \mapsto \mathbf{B}_2(s)U^2_{\mathbf{B}}(s,0)\mathbf{B}^{-\alpha}_{2,n}(0)$, for fixed $t \in (s,T]$ is continuous in the uniform topology with $\left\|\mathbf{B}_2(s)U^2_{\mathbf{B}}(s,0)\mathbf{B}^{-\alpha}_{2,n}(0)\right\|_{\mathbf{X_B}} \leq \mathrm{k}_{suf}|s|^{\alpha-1} \in L^1([0,t])$. Moreover, $\mathbf{B}_2(s)U^2_{\mathbf{B}}(s,0)\mathbf{B}_2^{-\alpha}(0) \overset{n\to\infty}{\to} \mathbf{B}_2(s)U^2_{\mathbf{B}}(s,0)\mathbf{B}_2^{-\alpha}(0)$ in the strong topology.

we can pass to the limit $n \to \infty$ on both sides of (40) and use Lebesgue's dominated convergence to get

$$\mathbf{B}^{\beta}_1(t)\big(U^1_{\mathbf{B}}(t,0) - U^2_{\mathbf{B}}(t,0)\big)\mathbf{B}_2^{-\alpha}(0) = \int_0^t \mathbf{B}^{\beta}_1(t)U^1_{\mathbf{B}}(t,s)\mathbf{B}^{1-\nu}_1(s)\mathbf{B}^{\nu}_1(s)[\mathbf{B}^{-1}_1(s) - \mathbf{B}^{-1}_2(s)] \quad (41)$$
$$\times\, \mathbf{B}_2(s)U^2_{\mathbf{B}}(s,0)\mathbf{B}_2^{-\alpha}(0)\, ds, \quad (42)$$

from which follows

$$\|\mathbf{B}^{\beta}_1(t)[\big(U^1_{\mathbf{B}}(t,0) - U^2_{\mathbf{B}}(t,0)\big)\mathbf{B}_2^{-\alpha}(0)\|_{\mathcal{L}(\mathbf{X_B})} \leq \mathrm{k}_{suf}\int_0^t (t-s)^{\nu-\beta-1}s^{\alpha-1}\|\mathbf{v}^{3,4}_1(s) - \mathbf{v}^{3,4}_2(s)\|_{\mathbf{X_B}}ds.$$

This in turn implies that

$$\begin{aligned}\|\mathbf{B}^{\beta}_1(t)[\big(U^1_{\mathbf{B}}(t,0) - U^2_{\mathbf{B}}(t,0)\big)u_0]\|_{\mathbf{X_B}} &\leq \|\mathbf{B}^{\beta}_1(t)[\big(U^1_{\mathbf{B}}(t,0) - U^2_{\mathbf{B}}(t,0)\big)]\mathbf{B}^{-\alpha}\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{B}^{\alpha}u_0\|_{\mathbf{X_B}}\\ &\leq \mathrm{k}_{suf}\|\mathbf{B}^{\alpha}u_0\|_{\mathbf{X_B}}\int_0^t (t-s)^{\nu-\beta-1}s^{\alpha-1}\|\mathbf{v}^{3,4}_1(s) - \mathbf{v}^{3,4}_2(s)\|_{\mathbf{X_B}}ds\end{aligned} \quad (43)$$

Term2: Using the Yosida approximation $\mathbf{B}_n(t)$ of $\mathbf{B}(t)$ and its associated evolution operator $U_n(t)$ along with Lebesgue's dominated convergence, we get that

$$\int_0^t \mathbf{B}^{\beta}_1(t)[\big(U^1_{\mathbf{B}}(t,s) - U^2_{\mathbf{B}}(t,s)\big)\mathbf{f}^1_s]ds = \int_0^t \mathbf{B}^{\beta}_1(t)U^1_{\mathbf{B}}(t,\tau)\mathbf{B}_1(\tau)[\mathbf{B}^{-1}_1(\tau) - \mathbf{B}^{-1}_2(\tau)]$$
$$\times\Big(\mathbf{B}_2(\tau)\int_0^{\tau} U^1(\tau,s)\mathbf{f}(s)ds\Big)\, d\tau. \quad (44)$$

where we re-expressed the integral on the right hand side by changing the order of integration. The term $\mathbf{B}_2(\tau)\int_0^{\tau} U^1(\tau,s)\mathbf{f}(s)ds$ can be estimated as follows:

$$\begin{aligned}\mathbf{B}_2(\tau)\int_0^{\tau} U^1(\tau,s)\mathbf{f}(s)ds &= \int_0^{\tau}\mathbf{B}_2(\tau)U^1(\tau,s)\mathbf{f}(s)ds\\ &= \int_0^{\tau}\mathbf{B}_2(\tau)U^1(\tau,s)[\mathbf{f}(s) - \mathbf{f}(t)]ds + \int_0^{\tau}\mathbf{B}_2(\tau)[U^1(\tau,s) - \mathrm{e}^{-(\tau-s)\mathbf{B}_2(\tau)}]\mathbf{f}(t)ds\\ &\quad + \int_0^{\tau}\mathbf{B}_2(\tau)\mathrm{e}^{-(\tau-s)\mathbf{B}_2(\tau)}\mathbf{f}(t)ds.\end{aligned}$$

By taking the $\mathbf{X_B}$ norm we get that

$$\begin{aligned}\left\|\mathbf{B}_2(\tau)\int_0^{\tau} U^1(\tau,s)\mathbf{f}(s)ds\right\|_{\mathbf{X_B}} &\leq \int_0^{\tau}\left\|\mathbf{B}_2(\tau)U^1(\tau,s)\right\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{f}(s) - \mathbf{f}(\tau)\|_{\mathbf{X_B}}ds\\ &\quad + \int_0^{\tau}\left\|\mathbf{B}_2(\tau)[U^1(\tau,s) - \mathrm{e}^{-(\tau-s)\mathbf{B}_2(\tau)}]\right\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{f}(\tau)\|_{\mathbf{X_B}}ds\\ &\quad + \left\|1 - \mathrm{e}^{-(\tau-s)\mathbf{B}_2(\tau)}\right\|_{\mathcal{L}(\mathbf{X_B})}\|\mathbf{f}(\tau)\|_{\mathbf{X_B}}\\ &= \text{tr1} + \text{tr2} + \text{tr3}\end{aligned}$$

$$\text{tr1} \leq \mathrm{k}_{suf}\int_0^{\tau}(\tau-s)^{\mu-1}s^{\alpha-\mu-1}ds\sup_{t,s\leq S}\frac{s^{1-\alpha-\mu}\|\mathbf{f}(\tau) - \mathbf{f}(s)\|_{\mathbf{X_B}}}{(\tau-s)^{\mu}} \leq \tau^{\alpha-1}\beta(\mu,\alpha-\mu)\|\mathbf{f}\|_{F^{\alpha,\mu}}$$

$$\text{tr2} \leq \mathrm{k}_{suf}\int_0^{\tau}(\tau-s)^{\mu+\nu-1-1}s^{\alpha-1}ds\sup_{t\leq S}s^{1-\alpha}\|\mathbf{f}(t)\|_{\mathbf{X_B}} \leq \mathrm{k}_{suf}\tau^{\mu+\nu+\alpha-2}\beta(\mu+\nu-1,\alpha)\|\mathbf{f}\|_{F^{\alpha,\mu}}$$

$$\text{tr3} \leq \mathrm{k}_{suf}\tau^{\alpha-1}\sup_{\tau\leq S}\tau^{1-\alpha}\|\mathbf{f}(\tau)\|_{\mathbf{X_B}} \leq \mathrm{k}_{suf}\tau^{\alpha-1}\|\mathbf{f}\|_{F^{\alpha,\mu}},$$

where β denotes the Euler-Beta function $\beta(m,n) = \int_0^1 x^{m-1}(1-x)^{n-1}dx$, with $m,n > 0$. Altogether, we get that

$$\left\|\mathbf{B}_2(\tau)\int_0^{\tau} U^1(\tau,s)\mathbf{f}(s)ds\right\|_{\mathbf{X_B}} \leq \mathrm{k}_{suf}\tau^{\alpha-1}\|\mathbf{f}\|_{F^{\alpha,\mu}}.$$

As a result (44) can be estimated as

$$\Big\| \int_0^t \mathbf{B}_1^\beta(t)[\big(U_{\mathbf{B}}^1(t,s) - U_{\mathbf{B}}^2(t,s)\big)\mathbf{f}_s^1]ds \Big\|_{\mathbf{X_B}}$$
$$\leq \mathrm{k}_{suf} \|\mathbf{f}\|_{F^{\beta'},\mu} \int_0^t (t-s)^{\nu-\beta-1} s^{\alpha-1} \|\mathbf{v}_1^{3,4}(s) - \mathbf{v}_2^{3,4}(s)\|_{\mathbf{X_B}} ds. \quad (45)$$

Term3:

$$\int_0^t \|\mathbf{B}_1^\beta(t)[U_{\mathbf{B}}^2(t,s)\big(\mathbf{f}_s^1 - \mathbf{f}_s^2\big)]\|_{\mathbf{X_B}} ds$$
$$\overset{\nu=1}{\leq} \mathrm{k}_{suf} T^{1-\alpha} \int_0^t (t-s)^{\nu-\beta-1} s^{\alpha-1} \|\mathbf{v}_1^{3,4}(s) - \mathbf{v}_2^{3,4}(s)\|_{\mathbf{X_B}} ds. \quad (46)$$

Thus from (43), (45) and (46) we get that

$$\|\mathbf{B}^\beta[\Psi_t^1 - \Psi_t^2]\|_{\mathbf{X_B}} \leq \mathrm{k}_{suf}(2 + T^{1-\alpha}) t^{\mu+\alpha-\beta+\nu-1} \|\mathbf{v}_1^{3,4} - \mathbf{v}_2^{3,4}\|_{C_0^\mu} \overset{\nu=1}{\leq} \mathrm{k}_{suf} t^{\alpha-\beta} t^\mu \|\mathbf{v}_1^{3,4} - \mathbf{v}_2^{3,4}\|_{C_0^\mu}$$
$$\Rightarrow \|\Psi^1 - \Psi^2\|_{B_{\mathbf{Z}^{3,4}_{\beta'}}} \leq \mathrm{k}_{suf} T^{\alpha-\beta} t^\mu \|\mathbf{v}_1^{3,4} - \mathbf{v}_2^{3,4}\|_{C_0^\mu}. \quad (47)$$

By the same computations we can also arrive at

$$\|\Psi^1 - \Psi^2\|_{C_0^\mu} \leq \mathrm{k}_{suf} T^{\alpha-\beta} \|\mathbf{v}_1^{3,4} - \mathbf{v}_2^{3,4}\|_{C_0^\mu}. \quad (48)$$

The estimates (47) and (48) are valid for every $\omega \in \Omega$, thus by taking the $L^2(\Omega)$ norm we get

$$\|\Psi^1 - \Psi^2\|_{\mathcal{Z}^{3,4}} \leq \mathrm{k}_{\mathcal{Z},C,H_e} T^{\alpha-\beta} \|\mathbf{v}_1^{3,4} - \mathbf{v}_2^{3,4}\|_{\mathcal{Z}^{3,4}}. \quad (49)$$

Contraction of Φ^1: Now consider the mapping $\Psi : \mathcal{K} \cap \mathcal{Z} \to \mathcal{Z}$ where

$$\Psi_t^k := \Psi(\mathbf{v}_t^k) = \Phi^1(\mathbf{v}_t^k) \quad \text{and} \quad f_t^k := f(\mathbf{v}_t^k) := r^1(\mathbf{v}^k)$$

$$\Psi_t^1 - \Psi_t^2 = \big(U_{A_1}^1(t,0) - U_{A_1}^2(t,0)\big)u_0 + \int_0^t \big(U_{A_1}^1(t,s) - U_{A_1}^2(t,s)\big) f_s^1 ds + \int_0^t U_{A_1}^2(t,s)\big(f_s^1 - f_s^2\big) ds$$
$$= \text{Term1} + \text{Term2} + \text{Term3}$$

By standard estimates we obtain

Term1:

$$\sup_{t\in[0,T]} \|(U_{A_1}^1(t,0) - U_{A_2}^1(t,0))\|_Y \leq \|C^1 - C^2\|_{C_0^\mu} T^{\mu+1}\, \mathrm{M}_J \sup_{t\in[0,T]} |\xi_t|\ \mathrm{e}^{2\mathrm{M}_J \int_0^t \sup_{r\in[0,T]} |\xi_r| dr}$$
$$\Rightarrow \mathbb{E}\|(U_{A_1}^1 - U_{A_2}^1)u_0^1\|_{B_Y}^2 \overset{(83)}{\leq} T^{2(\mu+1)} \mathrm{k}_{\xi_T} \mathrm{e}^{16 \mathrm{k}_{\xi_T}^2} \|u_0^1\|_Y^2 \|C^1 - C^2\|_{C_0^\mu}^2. \quad (50)$$

Term2:

$$\Big\| \int_0^t \big(U_{A_1}^1(t,s) - U_{A_1}^2(t,s)\big) f_s^1 ds \Big\|_Y \leq \sup_{0\leq s<t\leq T} \big\|U_{A_1}^1(t,s) - U_{A_1}^2(t,s)\big\|_Y \|f^1\|_{B_Y}\, t$$

This implies

$$\mathbb{E} \sup_{t\in[0,T]} \Big\| \int_0^t \big(U_{A_1}^1(t,s) - U_{A_1}^2(t,s)\big) f_s^1 ds \Big\|_Y^2 \leq \mathbb{E}\Big[\Big(\sup_{0\leq s<t\leq T} \big\|U_{A_1}^1(t,s) - U_{A_1}^2(t,s)\big\|_Y\Big)^2\Big] \|f^1\|_Y^2\, T^2$$
$$\overset{(50)}{\leq} T^{2(\mu+2)} \mathrm{k}_{\xi_T} \mathrm{e}^{16 \mathrm{k}_{\xi_T}^2} \|f^1\|_{B_Y}^2 \|C^1 - C^2\|_{C_0^\mu}^2. \quad (51)$$

Term3:

$$\begin{aligned}\Big\| \int_0^t U^2_{A_1}(t,s)\big(f^1_s - f^2_s\big)ds\Big\|_Y &\leq \int_0^t \|U^2_{A_1}(t,s)\|_Y \|f^1_s - f^2_s\|_Y ds \\ &\leq \int_0^t \|U^2_{A_1}(t,s)\|_Y \|f^1_s - f^2_s\|_Y ds \\ &\leq \sup_{s\in[0,T]}\bigg(\sup_{r\in[s,T]}\big\|U^2_{A_1}(t,r)\big\|_Y \sup_{r\in(0,s]}\frac{\|f^1_r - f^2_r\|_Y}{r^\mu}\bigg)\int_0^t s^\mu ds \\ &\leq \sup_{0\leq s<t\leq T}\big\|U^2_{A_1}(\cdot,0)\big\|_Y \|f^1 - f^2\|_{C^\mu_0}\int_0^t s^{2\mu}ds.\end{aligned}$$

This implies that

$$\begin{aligned}\sup_{t\in[0,T]}\Big\| \int_0^t U^2_{A_1}(t,s)\big(f^1_s - f^2_s\big)ds\Big\|_Y &\leq \sup_{0\leq s<t\leq T}\big\|U^2_{A_1}(\cdot,0)\big\|_Y \|f^1 - f^2\|_{C^\mu_0}\sup_{t\in[0,T]}\int_0^t s^\mu ds \\ \Rightarrow \mathbb{E}\Big\| \int_0^t U^2_{A_1}(t,s)\big(f^1_s - f^2_s\big)ds\Big\|^2_{B_Y} &\leq \mathbb{E}\Big[\Big(\sup_{0\leq s<t\leq T}\big\|U^2_{A_1}(t,s)\big\|_Y\Big)^2\Big]\|f^1 - f^2\|^2_{C^\mu_0}T^{2(\mu+1)} \\ &\leq T^{2(\mu+1)}\mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}^2_{\xi_T}}\|f^1 - f^2\|^2_{C^\mu_0}. \end{aligned} \tag{52}$$

Thus from (50), (51) and (52), we get that

$$\mathbb{E}\|\Psi^1 - \Psi^2\|^2_{B_Y} \leq \mathrm{k}_{suf}T^{2(\mu+1)}\mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}^2_{\xi_T}}\|\mathbf{v}^1 - \mathbf{v}^2\|^2_{C^\mu_0}. \tag{53}$$

By the same computations we also arrive at

$$\mathbb{E}\|\Psi^1 - \Psi^2\|^2_{C^\mu_Z} \leq \mathrm{k}_{suf}T^{2}\mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}^2_{\xi_T}}\|\mathbf{v}^1 - \mathbf{v}^2\|^2_{C^\mu_0}. \tag{54}$$

Thus, from (53) and (54) we get that

$$\|\Psi^1 - \Psi^2\|_{\mathcal{Z}^1} \leq T\,\mathrm{k}_{\mathcal{Z},H_i}\|\mathbf{v}^1 - \mathbf{v}^2\|_{\mathcal{Z}}. \tag{55}$$

Contraction of Φ^2: Consider the mapping $\Psi : \mathcal{K}\cap\mathcal{Z} \to \mathcal{Z}$, where

$$\Psi^k_t := \Psi(\mathbf{v}^k_t) = \Phi^2(\mathbf{v}^k_t) \quad\text{ and }\quad f^k_t := f(\mathbf{v}^k_t)$$

$$\begin{aligned}\|\Psi^1_t - \Psi^2_t\|_Y &\leq \|\mathrm{e}^{\int_0^t A^1_2(s)ds} - \mathrm{e}^{\int_0^t A^1_2(s)ds}\|_Y\|u_0\|_Y \\ &\leq \int_0^t \|A^1_2(s) - A^2_2(s)\|_Y ds)\mathrm{e}^{\int_0^t 2\|A_2\|_Y ds}\|u_0\|_Y \\ &\leq \bigg(\int_0^t \mathrm{k}_{A_2}(\|v^2_1 - v^2_2\|_Y + \|v^3_1 - v^3_2\|_{Z_{\beta'}} + \|v^4_1 - v^4_2\|_{Z_{\beta'}})ds\bigg)\mathrm{e}^{2\mathrm{k}_{\Lambda_2}\mathrm{k}_C t}\|u_0\|_Y \\ &\leq \Big(\mathrm{k}_{A_2}\|\mathbf{v}^1 - \mathbf{v}^2\|_{C^\mu_0})\mathrm{e}^{2\mathrm{k}_{\Lambda_2}\mathrm{k}_C t}\|u_0\|_Y\Big)t^{\mu+1} \\ \Rightarrow \|\Psi^1 - \Psi^2\|_{B_Y} &\leq \Big(\mathrm{k}_{\Lambda_2,C}\|\mathbf{v}^1 - \mathbf{v}^2\|_{C^\mu_0}\mathrm{e}^{2\mathrm{k}_{\Lambda_2}\mathrm{k}_C t}\|u_0\|_Y\Big)T^{\mu+1}. \end{aligned} \tag{56}$$

Similarly, we also get

$$\|\Psi^1 - \Psi^2\|_{C^\mu_0} \leq \Big((\mathrm{k}_{\Lambda_2,C}\|\mathbf{v}^1 - \mathbf{v}^2\|_{C^\mu_0})\mathrm{e}^{2\mathrm{k}_{\Lambda_2}\mathrm{k}_C t}\|u_0\|_Z\Big)T. \tag{57}$$

Since the estimates (56) and (57) hold for each $\omega\in\Omega$, by taking the $L^2(\Omega)$ norm we obtain

$$\|\Psi^1 - \Psi^2\|_{\mathcal{Z}} \leq T\mathrm{k}_{\mathcal{Z},N}\|\mathbf{v}^1 - \mathbf{v}^2\|_{\mathcal{Z}}. \tag{58}$$

Theorem 4.8 (Local existence and uniqueness)**.** *let $(\Omega,\mathcal{A},\mathbb{P})$ be a complete probability space and $(\mathcal{A}_t)_{t\geq0}$ be a normal filtration with $\mathfrak{N}$ (the system of all $\mathbb{P}$-nullsets) contained in $\mathcal{A}_0$. Let $\xi\in L^2(\Omega;C([0,\infty);\mathbb{R}))$ be an $\mathcal{A}_t$ adapted Gaussian process with independent increments. For $n\in\{1,2,3\}$ let $\mathfrak{D}\subset\mathbb{R}^n$ be an open bounded domain with Lipschitz boundary. Let $p>n$ and the operator $\mathbf{A}$ be as in (4), with the involved coefficients a and g satisfying the conditions of Lemmas 4.6 and 4.7. Moreover, let $\mathbf{r}$ be as in Lemma 4.1, so that*

$\mathbf{r} : \mathcal{K} \to F^{1,\mu}([0,T]; Y \times Y \times \mathbf{X_B})$. *Finally, let* $1 = \alpha > \theta > \theta' > \beta > \beta'$, $2\beta' := 1 + \frac{n}{2p}$ *and* $\mathbf{u}_0^{3,4} \in D(\mathbf{B}_0)$, $\mathbf{u}_0^{1,2} \in Y \times Z$ *be either deterministic or independent of* $(\mathcal{A}_t)_{t\geq 0}$.
Then for each $\Xi \in \mathbb{R}_+^{12}$, *there exists an unique process* $(\mathbf{u}_t)_{t\geq 0} \in \mathcal{K}(T)$, *whose realizations solve the abstract Cauchy problem* (20) *in the pathwise sense (i.e. for a.e.* $\omega \in \Omega$*). Moreover, the paths* $\mathbf{u}(\omega)$ *satisfy the estimates* (35) *and* (33).

Proof. From Lemma 4.6 and Lemma 4.7 we get the existence of a unique approximative solution. From the estimates (49), (55) and (58) we get a time $T > 0$ such that the mapping $\Phi : \mathcal{K} \cap \mathcal{Z} \to \mathcal{K}$ has a unique fixed point $\mathbf{u} \in \mathcal{K}$. Thus $\mathbf{u}$ is a strong solution to the abstract Cauchy problem (20). The uniqueness of $\mathbf{u}$ follows from a topological argument, details of which are given below. ■

4.5 Uniqueness

Let $\mathbf{u}^1$ and $\mathbf{u}^2$ be two solutions to the equation (20). Then for a sufficiently small time horizon $0 < S < T$, by similar arguments like in contraction, we get that

$$\begin{aligned} \|\mathbf{u}^1 - \mathbf{u}^2\|_{\mathcal{Z}} &\leq \mathrm{k}_{suf} S \|\mathbf{u}^1 - \mathbf{u}^2\|_{\mathcal{Z}} \\ \|\mathbf{u}^1 - \mathbf{u}^2\|_{\mathcal{Z}} (1 - \mathrm{k}_{suf} S) &\leq 0. \end{aligned} \tag{59}$$

This implies that, the term $\|\mathbf{u}^1 - \mathbf{u}^2\|_{\mathcal{Z}}$ is zero. Thus $\mathbf{u}^1$ and $\mathbf{u}^2$ are identical in the neighbourhood of 0, i.e. on $(0, S]$. Now, if we are able to extend this interval to the interval of existence $(0, T]$, then we get the uniqueness of the local solution.
The extension can be achieved using the following topological result: For a connected topological space X, if $Y \subseteq X$ is both open and closed in X then either $Y = \emptyset$ or $Y = X$. To this end let

$$\mathcal{O} := \{s \in (0, T] : \mathbf{u}^1 = \mathbf{u}^2 \text{ in } [0, s]\}.$$

Firstly, $\mathcal{O}$ is non-empty since $S \in \mathcal{O}$. Now we claim $\mathcal{O}$ is open and closed in $(0, T]$.

$\mathcal{O}$ open in $(0, T]$: Let $\hat{t} = t - S$. Then, since $\mathbf{u}^1(S) = \mathbf{u}^2(S)$, by (59) we get a new interval of uniqueness $(S, 2S] \subset (0, T]$, thus there exists a $(0, T]$-neighbourhood of S in $\mathcal{O}$. Analogously, for every $s \in \mathcal{O}$, there exists a $(0, T]$-neighbourhood of S is in $\mathcal{O}$. Thus, $\mathcal{O}$ is open in $(0, T]$.

$\mathcal{O}$ closed in $(0, T]$: Let $(s_n)_{n\in\mathbb{N}} \subset \mathcal{O}$ be a sequence converging to s in $(0, T]$. Then there exists $\mathbb{N} \ni N(\epsilon) < \infty$ such that for all $m > N$, we have that $|s_m - s| < \epsilon$. Since $s_m \in \mathcal{O}$, $\mathbf{u}^1 = \mathbf{u}^2$ on $(0, s_m]$, thus we can define a new interval $(s_m, s]$ for which (59) holds.
Consequently, $\mathbf{u}^1 = \mathbf{u}^2$ on $(s_m, s]$ and also on $(0, s]$, thus $s \in \mathcal{O}$.
Altogether, we have that $\mathcal{O} = (0, T]$ and $\mathbf{u} = \mathbf{u}^1 = \mathbf{u}^1$ is a unique solution to (20) in $\mathcal{K}$(T).

Remark 1. *Note that since the domain* $\mathfrak{D}$, *the parameters, the coefficients, and the initial values are real, if* $\mathbf{u}$ *solves* (20) *then so does its conjugate* $\bar{\mathbf{u}}$. *But the uniqueness implies that* $\mathbf{u} = \bar{\mathbf{u}}$, *thus the solution* $\mathbf{u}$ *is real valued.*

4.6 Global existence

Since the interval $(0, T]$ for the existence of a unique local solution is closed (relatively to $(0, \infty)$) and the a priori estimates are in principle only dependent on the difference between the initial and final times, we can extend the local solution $u \in \mathcal{K}(T)$ to the abstract Cauchy problem (20) in a unique way to any arbitrary time interval $(0, \mathbb{T}] \subset (0, \infty)$.
Indeed, consider the abstract Cauchy problem

$$\left.\begin{aligned} \frac{d}{dt}\mathbf{v}_t(\omega) + \mathbb{A}(\mathbf{v}_t(\omega))\mathbf{v}_t(\omega) = \mathbf{r}(\mathbf{v}_t(\omega)), \qquad \text{on } \mathbf{X},\ \ t \in (t_1, T_1] \\ \mathbf{v}_{t_1}(\omega) = \mathbf{v}_1(\omega). \end{aligned}\right\} \tag{60}$$

Let $t_1 < T$ and $\mathbf{v}_1(\omega) := \mathbf{u}_{t_1}(\omega)$, where $\mathbf{u}_t \in \mathcal{K}(T)$ is the unique solution to the Cauchy problem (20). Now letting $\tau := t - t_1$ we can reformulate the problem on the interval $[0, T_1 - t_1]$, for which we can apply Theorem (4.8) to get the existence of a unique solution $\mathbf{v}_\tau \in \mathcal{K}(T_1 - t_1)$ on the interval $[t_1, T_1]$. Due to uniqueness, $\mathbf{v}_t(\omega) = \mathbf{u}_t(\omega)$ for $t \in [t_1, T]$, which in turn ensures that the extension preserves the regularity with respect to the time variable. However, one should note that in order to apply the local existence theorem, we cannot directly rely on the estimates (38) and (50). Instead, we have to use (87) in the estimation step (37) and (50) to be able to express $\mathbb{E}[\|U_{A_1}(\omega, t_2, t_1)u^1_{t_1}\|]$ as $\mathbb{E}\|U_{A_1}(\omega, t_2, t_1)\|]\mathbb{E}[\|u^1_{t_1}\|]$ plus some remainder terms. This increases the upper bound, therefore every extension step N may require larger constants P_1^N, P_2^N and P_3^N to represent the local bounds. Nevertheless, this allows us to inductively extend the interval of existence to an arbitrary finite time interval $[0, \mathbb{T}] \subset [0, \infty)$, with $\mathbb{T} \leq NT$, for some $N \in \mathbb{N}$.

4.7 Non-negativity of the local solution:

Since neither is the sectorial operator $\mathbf{B}$ symmetric nor is the off-diagonal operator B_2 a positive operator, it is nontrivial to prove the resolvent positivity of $\mathbf{B}$, which would be a sufficient condition for the positivity of the evolution operator. Instead, we resort to standard L^2 estimates for proving the non-negativity of u^3 and u^4.

Lemma 4.9. *u^3 is non-negative.*

Proof. Consider the equation

$$\partial_t u^3 = J(u^4)T(u^1,u^3) - q_2 u^3 + \Delta u^3 + \nabla\cdot(g\nabla u^4) + \nabla\cdot(h\nabla u^2) \tag{61}$$

In the following we will denote $w^- := \min(w,0)$ for any function w. In view of the estimates in Section 4.4 we have $\mathbf{u}\in\mathcal{K}(T)$, thus the right hand side of (61) is finite in the $L^p(\mathfrak{D})$-norm and it holds that

$$\begin{aligned}\int_{\mathfrak{D}} \partial_t u\, u^- dx = \int_{supp(u^-)} \partial_t u\, u^- dx &= \frac{1}{2}\int_{supp(u^-)} \partial_t (u^-)^2 dx\\ &= \frac{1}{2}\frac{d}{dt}\int_{supp(u^-)} (u^-)^2 dx = \frac{1}{2}\frac{d}{dt}\int_{\mathfrak{D}} (u^-)^2 dx\end{aligned} \tag{62}$$

Assume $u^3 \neq 0$. Then, multiplying (61) with $u^{3,-}$ and taking the $L^2(\mathfrak{D})$ inner product we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|u^{3,-}\|_2^2 &= (JT\,,u^{3,-}) - q_2\|u^{3,-}\|_2^2 - \|\nabla u^{3,-}\|_2^2 + (\nabla\cdot g\nabla u^4, u^{3,-}) + (\nabla\cdot h\nabla u^2, u^{3,-})\\
&\le \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 - \tilde{q}_2\|u^{3,-}\|_{H^1}^2 + (\nabla\cdot g\nabla u^4, u^{3,-}) + (\nabla\cdot h\nabla u^2, u^{3,-})\\
&\le \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 - (\nabla u^4, g\nabla u^{3,-}) - (\nabla u^2, h\nabla u^{3,-})\\
&= \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 - (\nabla u^4, \hat{g}u^3\nabla u^{3,-}) - (\nabla u^2, \hat{h}u^3\nabla u^{3,-}), \quad g := u^3\hat{g} \text{ and } h := u^3\hat{h}.\\
&= \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 - (\nabla u^4, \hat{g}\frac{1}{2}\nabla(u^{3,-})^2) - (\nabla u^2, \hat{h}\frac{1}{2}\nabla(u^{3,-})^2)\\
&= \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 + \frac{1}{2}(\nabla\cdot\hat{g}\nabla u^4, (u^{3,-})^2) + \frac{1}{2}(\nabla\cdot\hat{h}\nabla u^2, (u^{3,-})^2)\\
&\le \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 + \frac{1}{2}\big(\|\nabla\hat{g}\cdot\nabla u^4\|_2 + \mathrm{M}_g\|\Delta u^4\|_2 + \|\nabla\hat{h}\cdot\nabla u^2\|_2 + \mathrm{M}_h\|\Delta u^2\|_2\big)\|u^{3,-}\|_2^2\\
&\le \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 + \frac{1}{2}\big(\|\nabla\hat{g}\|_4^2\|\nabla u^4\|_4^2 + \mathrm{M}_g\|\Delta u^4\|_2 + \|\nabla\hat{h}\|_4^2\|\nabla u^2\|_4^2 + \mathrm{M}_h\|\Delta u^2\|_2\big)\|u^{3,-}\|_2^2\\
&\le \mathrm{M}_J\mathrm{M}_T\|u^{3,-}\|_2^2 + \frac{1}{2}\big(\|\hat{g}\|_{H^1_{2p}(\mathfrak{D})}^2\|u^4\|_{H^2_p(\mathfrak{D})}^2 + \mathrm{M}_g\|u^4\|_{H^2_p(\mathfrak{D})}\\
&\qquad\qquad + \|\hat{h}\|_{H^1_{2p}(\mathfrak{D})}^2\|u^2\|_{H^2_p(\mathfrak{D})}^2 + \mathrm{M}_h\|u^2\|_{H^2_p(\mathfrak{D})}\big)\|u^{3,-}\|_2^2\\
&\le \mathrm{k}_{\hat{g}\hat{h}}(t)\|u^{3,-}\|_2^2,\\
\Rightarrow \|u^{3,-}\|_2^2 &\le \|u_0^{3,-}\|_2^2\, \mathrm{e}^{\int_0^t \mathrm{k}_{g,u^4}(s)ds},\end{aligned} \tag{63}$$

where

$$\mathrm{k}_{\hat{g}\hat{h}} := \mathrm{M}_J\mathrm{M}_T + \frac{1}{2}\big(\|\hat{g}\|_{H^1_{2p}(\mathfrak{D})}^2\|u^4\|_{H^2_p(\mathfrak{D})}^2 + \mathrm{M}_g\|u^4\|_{H^2_p(\mathfrak{D})} + \|\hat{h}\|_{H^1_{2p}(\mathfrak{D})}^2\|u^2\|_{H^2_p(\mathfrak{D})}^2 + \mathrm{M}_h\|u^2\|_{H^2_p(\mathfrak{D})}\big) < \infty.$$

Thus $u^{3,-}(t)$ is equal to zero for all $t>0$ if $u_0^{3,-}=0$. This implies that if u_0^3 is non-negative then u^3 stays that way for all $t>0$. ■

Lemma 4.10. *u^4 is non-negative and bounded by the constant function* 1.

Proof. Consider the following equation:

$$\partial_t u^4(t) = u^4(1-u^4)(\Lambda_1+\Lambda_2) + \nabla\cdot(a\nabla u^4) - b\nabla u^3\cdot\nabla u^4. \tag{64}$$

We apply an argument similar to that used in the previous lemma. Multiplying (64) with $u^{4,-}$ and integrating over $\mathfrak{D}$ we get

$$\begin{aligned}
\frac{d}{dt}\|u^{4,-}\|_2^2 &\leq (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 - \|\sqrt{a}\nabla u^{4,-}\|_2^2 - (b\nabla u^3\cdot\nabla u^4, u^{4,-})\\
&= (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 - \|\sqrt{a}\nabla u^{4,-}\|_2^2 - (b\nabla u^3, \frac{1}{2}\nabla(u^{4,-})^2)\\
&= (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 - \|\sqrt{a}\nabla u^{4,-}\|_2^2 + \frac{1}{2}(\nabla\cdot b\nabla u^3, (u^{4,-})^2)\\
&\leq (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 + \frac{1}{2}(\|\nabla b\cdot\nabla u^3\|_2 + \|b\Delta u^3\|_2)\|u^{4,-}\|_2^2\\
&\leq (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 + \frac{1}{2}(\|\nabla b\|_4^2\|\nabla u^3\|_4^2 + \mathrm{M}_b\|\Delta u^3\|_2)\|u^{4,-}\|_2^2\\
&\leq (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2 + \frac{1}{2}(\|b\|^2_{H^1_{2p}(\mathfrak{D})}\|u^3\|^2_{H^2_p(\mathfrak{D})} + \mathrm{M}_b\|u^3\|_{H^2_p(\mathfrak{D})})\|u^{4,-}\|_2^2\\
&\leq \mathrm{k}_{b\Lambda_{12}}(t)\|u^{4,-}\|_2^2
\end{aligned}$$

$$\Rightarrow \|u^4\|_2^2 \leq \|u_0^{4,-}\|_2^2\, \mathrm{e}^{\int_0^t \mathrm{k}_{b\Lambda_{12}}(s)ds}.$$

$$\mathrm{k}_{b\Lambda_{12}}(t) := (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|u^4\|_{H^2_p(\mathfrak{D})}) + \frac{1}{2}(\|b\|^2_{H^1_{2p}(\mathfrak{D})}\|u^3\|^2_{H^2_p(\mathfrak{D})} + \mathrm{M}_b\|u^3\|_{H^2_p(\mathfrak{D})}).$$

Thus $u^4(t)\geq 0$, for all $t>0$ if $u_0^4\geq 0$.
Now let $w := 1-u^4$ and $w_0 = 1-u_0^4$; then w satisfies the following equation

$$\frac{d}{dt}w(t) = w(1-w)(-\Lambda_2-\Lambda_1) + \nabla\cdot(a\nabla w) - b\nabla u^3\cdot\nabla w.$$

Multiplying this equation with w^- we get

$$\begin{aligned}
\frac{d}{dt}\|w^-\|_2^2 &\leq (\mathrm{M}_{\Lambda_2}+\mathrm{M}_{\Lambda_1})(1+\|w\|_{H^2_p(\mathfrak{D})})\|w^-\|_2^2 - \|a\nabla w^-\|_2^2 - (b\nabla u^3\cdot\nabla w, w^-)\\
&\leq \mathrm{k}_{b\Lambda_{12}}(t)\|w^-\|_2^2\\
\Rightarrow \|w\|_2^2 &\leq \|w_0^-\|_2^2\, \mathrm{e}^{\int_0^t \mathrm{k}_{b\Lambda_{12}}(s)ds}.
\end{aligned}$$

Thus $w\geq 0$ for all $t>0$ if $w_0\geq 0$. This implies that $u^4\leq 1$ for all $t>0$ if $u_0^4\leq 1$. ■

Lemma 4.11. *The solution u^1 in non-negative and u^2 is in the interval $[0,1]$.*

Proof. In virtue of the assumptions in Subsection 3.1 and due to the continuity of the state-dependent noise, we get that $u^1=0$ is a steady state and it is unstable, since $R_1(H_i,\cdot,\cdot)>0$ in the neighborhood of 0.
Similarly, observe that $R_4(\cdot,\cdot,0)=0$, hence $u^2=0$ is a steady state. Moreover, $R_4(\cdot,\cdot,1)<0$ implies that $R_4(\cdot,\cdot,1)<0$ in the neighborhood of $N=1$, as $H_e(t,x)$ and $C(t,x)$ are continuous. Thus, $u^2\leq 1$ if $u_0^2\leq 1$ and the non-negativity of u^2 follows from $u^2=0$ being a steady state. ■

5 Numerical simulations

In this section we perform numerical simulations for the proposed model (2) in order to assess the influence of acidity on the tumor behavior. The simulations are done both in one-dimensional (1D) and two-dimensional (2D) spatial domains: The former allow to better visualize the dynamics of the propagating wave fronts, while the latter are better suited to visualize the infiltrative growth patterns. In both cases we use the Ornstein-Uhlenbeck process $\xi_t := (O_t)_{t\geq 0}$, with

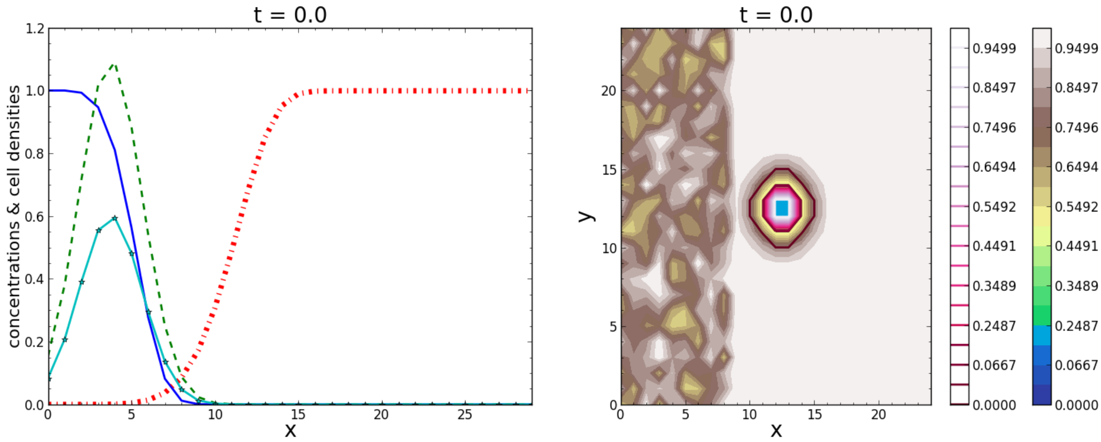
$$O_t = e^{-\nu t}O_0 + \mu(1-e^{-\nu t}) + \sigma\int_0^t e^{-\nu(t-s)}dW_s$$

as the noise process ξ_t, with the parameters given in Table 1. We use a RODE-Taylor scheme [21] for discretizing the intracellular proton dynamics equation (2a) and an implicit-explicit finite difference scheme for the rest of the equations. The parameters chosen for 1D and 2D simulations are given in Table 1, as well. The chosen initial conditions are as shown in Figure 9. For this and all subsequent pictures we will use the following legends:

- 1D simulations:
  Solid curve (——): cancer cell density C; dashed curve $(- - -)$: extracellular proton concentration H_e; barred curve (|||): normal cell density N, and solid line with asterisks (–⋆–⋆–): intracellular proton concentration H_i.
- 2D simulations: The solid curves (—) indicate the level sets of cancer cell density C, while filled regions indicate level sets of normal cell density N. The values corresponding to these level sets are indicated by the colorbars adjacent on the right side to the 2D plots. In order to see the effects of spatial heterogeneity, we have added some random perturbation to the initial value of the normal cell density only on the left side of the xy-plane. Thus, these perturbations are seen as patches on the left half of the plot (see Figure 9b).

Figure 9: Initial conditions in the 1D and 2D case

(a) Initial condition in the 1D case (b) Initial condition in the 2D case



Before we begin discussing the simulation results, for the sake of completeness we would like to give our exact choice of the repulsion, diffusion, advection, and other involved coefficients. All the variables H_i, H_e, C, N appearing in the below definitions are in non-dimensionalized form.

1. The repulsion coefficients $g(C, H_e, H_i)$ and $h(C, H_e)$ are defined as

$$g(C, H_e, H_i) := \frac{10(1 + 24H_i)e^{-H_i^2} C H_e}{1 + H_e^2 + C^2}, \tag{65}$$

$$h(N, H_e) := \frac{10 N H_e}{.1 + N^2 + H_e^2}. \tag{66}$$

2. The diffusion coefficient $a(H_i, H_e, C, N)$ is defined as follows:

$$a(C, N, H_e, H_i) := \max\left(\left(\frac{10(H_e - H_i)(H_e + 1.5)(H_i + .5)}{1 + (H_i + .5)^4 + (H_e + 1.5)^4 + (H_e - H_i)^4}\right) \times \left(\frac{C}{.001 + C + N}\right) - 0.3,\ 0.0\right) + 0.001 \tag{67}$$

3. The go, grow and recede functions $b(H_i, H_e)$, $\Lambda_1(H_e, H_i)$ and $\Lambda_2(H_e, H_i)$ are, respectively, defined as

$$b(H_i, H_e) := \max\Big(\Big(\big[G_2(H_i, H_e) - 0.04\big] - \big[G_1(H_i, H_e) - 0.2\big]\Big) - 0.22\,,\ 0\Big) \tag{68}$$

$$\Lambda_1(H_i, H_e) := \max\Big(- \Big(\big[G_2(H_i, H_e) - 0.04\big] - 10\big[G_1(H_i, H_e) - 0.2\big]\Big) - 0.65\,,\ 0\Big) \tag{69}$$

$$\Lambda_2(H_i, H_e) := \min\Big(\Big(\big[G_1(H_i, H_e) - 0.2\big] + 3\big[G_2(H_i, H_e) - 0.04\big]\Big) + 0.14\,,\ 0\Big). \tag{70}$$

where the auxiliary functions G_1 and G_2 are given by

$$G_1 := (H_e + .4)^2\, \mathrm{e}^{-3((H_i-1.6)^2+(H_e+.4)^2-2)^2}, \quad G_2 := \frac{4(H_i + 0.15)(H_e - 0.5)}{0.01 + (0.15 + H_i)^4 + (1.5 - H_e)^4}.$$

4. The flux modulation function $J(C)$ is defined as

$$J(C) := \frac{(C)(1.1 - C)}{(.599485 + (2C)^2 + (C)^4)}.$$

These coefficients satisfy the assumptions made in Section 3.1. We now begin our discussion of the simulation results.

5.1 1D simulations

Figures 10 -12 depict a temporal sequence of different sample paths of the solution. Several features can be inferred from these plots:

1. In all sample solutions the dynamics of H_i is dominant at the falling edge of C, i.e. near the tumor-stroma interface, exceeding the values it takes in the tumor bulk. Phenomenologically, this captures the high metabolic rates of the cells on the tumor edge to realize cytoskeleton remodeling and taxis, which results in acidic byproducts.
2. In all sample solutions the concentration of H_e exceeds that of H_i on the support on cancer cell density. This is in accordance to the reverse pH gradient observed in the tumor microenvironment. However, due to fluctuations in H_i (induced by the noise), it may happen that near the tumor-stroma interface, the concentration of H_i exceeds that of H_e for a brief period of time.
3. In all sample solutions the concentration of H_e is high at the interface between cancer and normal cells, which captures phenomenologically the accumulation of acid due to high metabolic rates. This accumulation influences in turn the dynamics at the population level in the following way:
   (a) Depending on the H_i and H_e concentrations, the cancer dynamics may be in either one of the go, grow, or recede modes: If the H_i, H_e values are in the support of b, then the cancer cells are in the go-mode, so the cells move in the direction of higher H_e. If the H_i, H_e values are in the support of Λ_1, then the cancer cells are in the grow-mode, hence the cells proliferate. Lastly, if the H_i, H_e values are in the support of Λ_2, the cancer cells are in the recede-mode, meaning a decay of tumor cell density.
   (b) Depending on γ_N, γ_{Λ_3} and γ_{Λ_4}, the depletion of normal cells varies based on the concentration of H_e and on the density of C. Thus according to the interplay between the go-grow-recede functions and the decay and remodelling rates of normal cells, we can expect appearance (opening) and disappearance (closing) of gaps between cancer and stromal cells.

The interplay between the parameters indicated in Table 2 results in the following trends for the gaps:

1. Figure 10 represents the time snapshots of the 90^{th} sample solution. There, a gap is beginning to form at time $t = 130$. It is not totally closed (i.e. no overlapping of cancer and normal cells happens), but forms a $\vee$-shaped profile with both cell densities being almost zero at the same spatial point. By the time point $t = 220$ the gap has been widened by the accumulated acid. When $t = 280$ (not shown) the gap has already begun to shrink and is finally closed at time $t = 455$. However, because of the overlap of cancer cell and normal cell, and the accumulated acid at the overlapping interface, the gap reappears at time $t = 500$. This alternating sequence of gap/no-gap happens for most of the sample paths and depicts the crawling/hopping/tumbling (shortly CHT) phenomenon of the tumor edge.
2. In Figure 11 representing the time snapshots of the 63^{rd} sample solution we see that at time $t = 430$ a secondary gap appears beyond the cancer-stroma interface resulting in a kind of isolated patch of normal cells. Such patches are even more prominent in the sample solution number 64 (Figure 12a), where we can observe two such islands at time $t = 475$. However, the one closest to the tumor edge gets wiped out due to the accumulated acid at round time $t = 500$. Such islands are a consequence of the competing growth and decay (Λ_4 and Λ_3) terms in normal cell dynamics. This dynamics is among the possible causes for infiltrative patterns.

Figure 10: Time snapshots of the sample solution 90, in the case of a 1D domain.

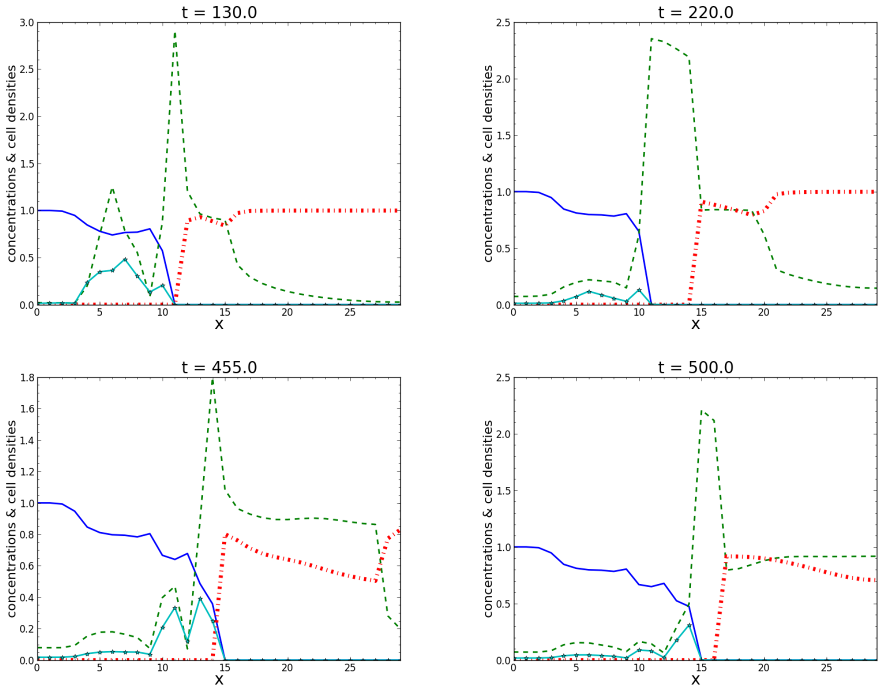


Figure 11: Time snapshots of the sample solution 63, in the case of a 1D domain.

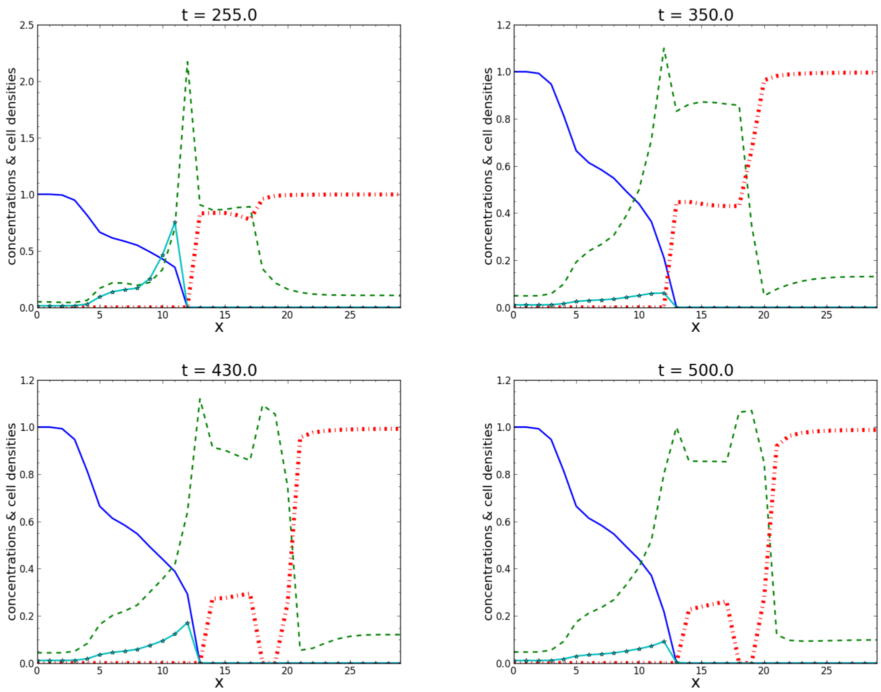
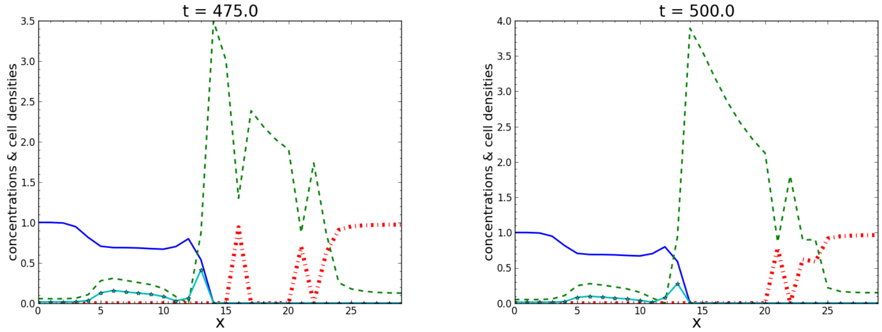
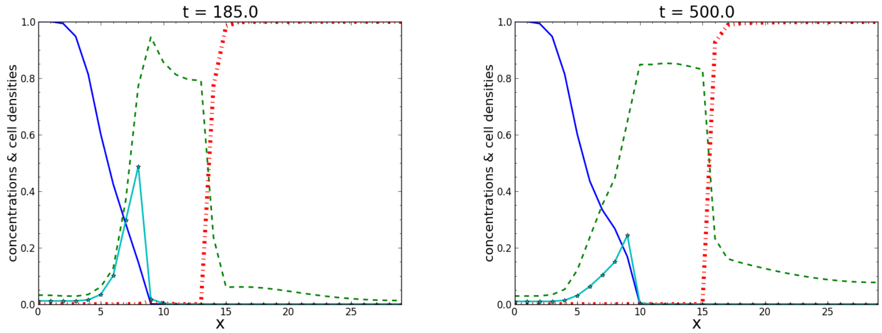


Figure 12: Time snapshots of the sample solutions 64 and 58, in the case of a 1D domain.

(a) Sample solution number 64



(b) Sample solution number 58



3. In contrast to above sample solutions where the cancer edge is progressing due to *go* and *grow* mechanisms, Figure 12b shows that the progression is halted due to the failure of the H_i and H_e to be in the support of the *go* or *grow* functions. Instead, they fall in the support of the *recede* function, thereby undergo decay and become unable to progress. As a result, the gap widens and remains unclosed till the end of the simulation.

4. Finally, averaging over the samples and looking at the numerical mean solution (Figure 13), we observe that the gap doesn't seem to appear, except at the beginning, for a minute time span. This is intuitively plausible, since the gaps (if they occur) are formed at different spatial points and at different times and are of different widths. Thus, on average no gaps seem to appear. However, the probability of gap formation can be increased by enhancing the normal cell decay rates and decreasing the normal cell remodeling rates, which results in wider and more frequently occurring gaps. Thereby, the gap can be observed even in the average behavior (Figure 13b).

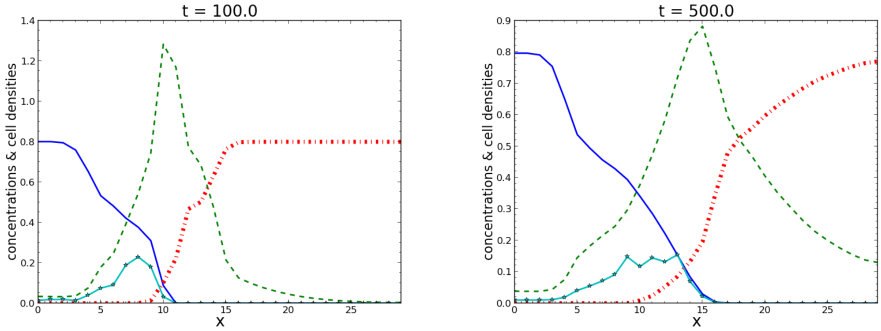
5.2 2D simulations

Figures 14 -17 depict time sequences of 5 different sample paths of the solution. The figures contain contour lines of cancer cell density overlapped with colored contour regions of normal cell density. To test the influence of spatial heterogeneity we perturb the initial condition of the normal cell density in such a way that it is smooth on the right three-quarters of the spatial plane and it is rough and uneven on the left quarter of the spatial plane. The initial condition is the same for all the sample solutions and is shown in Figure 9b. In each of the figures the first and third rows depict the level sets of cell densities. The solid curves (—) indicate the level sets of cancer cell density C, while filled regions indicate level sets of normal cell density N. The white regions appearing in the center are the gaps $\Big($regions of nearly zero cell density ($< 10^{-7}$)$\Big)$. The second and fourth rows show the level sets of extracellular proton concentration H_e. Concretely, the figures illustrate the following:

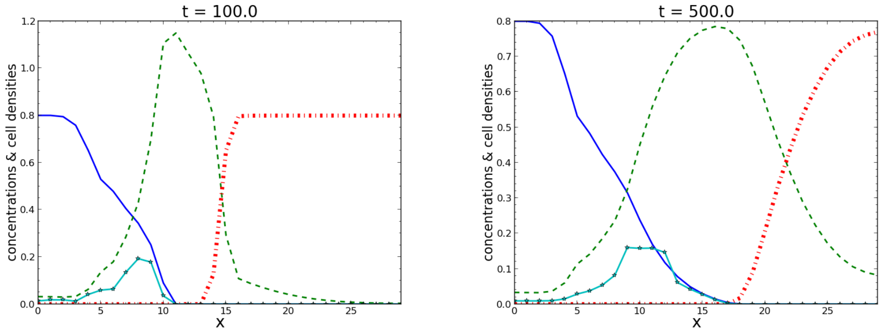
1. Figure 14 represents time snapshots of the 5th sample solution. At time $t = 6$ we see

Figure 13: Time snapshots of the expected values of sample solutions.

(a) Numerical expectation of sample solutions



(b) Numerical expectation of sample solutions for $\gamma_{\Lambda_3} = 1.1144$



rosette-like extensions of the tumor boundary (dark purple), while the inner core (pinkish-purple) is still circular and a small protrusion of the layers adjacent to the boundary towards the uneven side (left side of the xy-plane) of the stromal region becomes visible. At time $t = 49.5$, a gap is formed on the uneven side of the stroma, with the tumor boundary having a prominent bud-like protrusion into the uneven side of the stroma. By the time $t = 79.5$, the gap has widened and several cavities (pure white region surrounded by greenish-blue or blue region) and islands (greyish-white surrounded by brownish-grey region) are formed on the left side of the xy-plane. However, the right side of the xy-plane where the stroma is densely packed without irregularities, is still preserving the initial tissue structure. This is analogous to the observation made in the 1D case for sample number 64. Moreover, the tumor boundary has extended into the gap exhibiting small bud-like formations. By the time $t = 150$, the gap has extended with more islands and cavities appearing on the left side, with the tumor boundary bulging into the gap. The extension towards the smoother side of the stroma is similar to a CHT-like motion in the case of a 1D domain.

2. Figure 15 represents time snapshots of the 25th sample solution. At time $t = 22.5$ there are two spiked protrusions towards the left side, and they develop into a bulge at time $t = 90$. Also at the same time there are islands and cavities formed on the left side. At time $t = 120$, the gap has widened with the bulge being transformed into pointed protrusions. Also, there are bulges towards the top and bottom of the stroma. Finally, by the time $t = 150$ (figure not shown) the gap has widened even more, with the cancer boundary exhibiting a bulge towards the gap. For other sample paths (not shown here) a similar behavior can be observed, however with a relatively slow deterioration of the farther stroma region, leading to the lack of islands, but still exhibiting cavities.

3. More interestingly, in sample solution 100 (Figure 16) we see a turtle-shaped boundary being formed at time $t = 75$, which then transforms to let the left-most part of the tumor (the 'head of the turtle') ramify at time $t = 115.5$ and deforming into a protruding structure.

4. In contrast to the above sample solutions, in Figure 17 we see like in the 1D case that, due to rapid deterioration on the stroma, the progression of cancer is more or less

diffusion-like with the boundary moving in a rather homogeneous fashion, without prominent protrusions.

5. Averaging over the samples and looking at the numerical mean solution (Figure 19), we observe as in the 1D case that the gap doesn't seem to appear, except at the beginning, for a minute time span. However, for an increased normal cell decay rate we see a gap even in the average behavior (Figure 20).
6. The above patterns mainly represent the INFa class of infiltrative growth pattern [4]. To create INFb and INFc patterns, consider the case where γ_b and γ_{Λ_4} is relatively larger while γ_{Λ_3} is relatively smaller. Then the forming spikes/protrusions/buds overlap with the stromal region representing an infiltrative growth pattern of types INFb or INFc. This is clearly visible in Figure 18. We hypothesize that even more interesting patterns may be obtained by varying the parameters γ_N, $\gamma_{\Lambda_{4,1}}$, γ_{Λ_3} and γ_a.

6 Discussion

Acidity plays a pivotal role in the local invasiveness of a tumor. On the one hand it causes degradation of surrounding tissue and on the other hand it promotes tumor cell motility and proliferation. The invasiveness can be assessed by its infiltrative growth patterns, whose first stage is more or less characterized by the formation of gaps between the outer proliferating tumor edge and the retreating stroma. Several mathematical models have been proposed to access the local invasiveness of the cancer occurring mainly due to the acid dynamics, the first being perhaps that in [14], with a degenerate nonlinear setting. A slightly modified model was proposed in [30] by introducing a pure-decay-term of cancer cell density. In the former model, gap formation was predicted in aggressive tumors, while in the latter setting the gap formation was found to appear for less aggressive tumors.
Based on these observations we proposed in Section 2 a stochastic model for the formation of a gap by the acidic extracellular environment. In Section 3 we proved the well-posedness of the model, which cleared the way for 1D and 2D simulations. For the chosen parameter values, the 1D simulations highlight the following:

1. The acid dynamics is dominant mainly at the progressing front of the tumor, i.e. on the falling edge of the tumor density. This is due to the choice of the modulation function $J(C)$ attaining its maximum when the cancer density is far below its carrying capacity.
2. A reversed pH-gradient is observed on the support of cancer cell density, with at exception at the proliferating edge, which occurs in the case of large fluctuations in intracellular proton concentration. This feature is solely dependent on the strength of membrane transport flux and the intracellular acid-sequestration rate.
3. The repulsion terms in the extracellular proton dynamics result in the accumulation of acid at the rarely populated regions. The acid accumulated at the tumor-stroma interface leads to $\vee$-shaped or $\sqcup$-shaped or $\cup$-shaped gaps. Moreover, in case of non-uniform normal cell density (which is possible even if the initial value is smooth due to the remodeling term), acid may additionally accumulate at the distant parts of the stroma, thereby leading to the formation of cavities and islands. Here it is important to remark that the formation of the gap, cavities, and islands is sensitive to the migration and reaction parameters Ξ_M and Ξ_R, respectively, but also to the choice of the go-or-grow-or-recede (GGR) function. Although we have chosen these functions based on qualitative features, it would be practical to make coices that fit to experimental data.
4. Typically, the cancer edge keeps progressing, which pushes the acid further into the stromal region. This in turn results in their degradation, thereby forming the gap. However, the accumulated acid also enhances motility and proliferation; thereby, the tumor edge progresses towards the stromal region. The advancement of tumor and the retraction of stroma leads to an alternating sequence of gap and no-gap, representing a slow encroachment of the stromal region by the CHT type of movement.

For the chosen parameters, in the case of 2D simulations we have the following observations:

1. The heterogeneity of the stromal region has a very strong influence on the acid accumulation patterns. Larger γ_D combined with larger γ_g, γ_h result in quick accumulation of acid at some of the local valleys of the stromal region. Now depending

[4] see Section 1 for the notion of INF

Table 1: Simulation parameters

Parameters for OU-process O_t	
Mean μ	0
Variance σ	1
Mean reverting rate ν	.1
Initial value O_0	0

Numerical parameters		
	1D	2D
T (Total time)	500	150
M (# Monte Carlo simulations)	4000	100
τ (Temporal step size)	.1	.3
h_{x_1} (Spatial step size along x_1)	.1	.01
N_{x_1} (Grid resolution along x_1)	30	25
h_{x_2} (Spatial step size along x_2)	-	.01
N_{x_2} (Grid resolution along x_2)	-	25

on the choice of γ_{Λ_3} and γ_{Λ_4} the valleys become deeper and deeper, finally resulting in an island or a cavity. Thus, shallow valleys (if existing at time $t = 0$) are the probable sites for cavity formation and their surrounding area is a probable region for an island formation.

2. Heterogeneity of the stromal region also affects (indirectly) the deformations and protrusions of the tumor boundary. As mentioned above, the local valleys of the stromal regions are the probable sites of acid accumulation. This means that less acid is left at the tumor-stroma interface. Now depending of the choice of GGR functions, the cells at the tumor boundary may under undergo migration or proliferation or recession. Thus, quick deterioration of the normal cells near the stromal interface followed by diffusion and accumulation of acid at distant stromal region may result in a stagnant tumor or even in overall decay. This was indeed the case for sample solutions 49 (Figure 17) and 58 (Figure 12b) in the 2D and 1D case, respectively. This case, although of practical/clinical importance, is not visually appealing. Hence, in the case where the accumulated acid at the tumor interface is activating the go-or-grow function, we see protrusions and bud formation on the tumor edge. Moreover, we saw (in Figures **??**-**??**) that such spikes and buds were mainly in the direction of the forming gap, suggesting that cancer cells are directing their movement towards the space created by the acid. Finally, for a suitable choice of parameters γ_b and γ_{Λ_4}, the model could also reproduce protrusions overlapping with the stromal region, thus it represents to a fair extent the INFb and INFc classes of patterns.

In summary, for just a few choices of Ξ_M and Ξ_R, the model phenomenologically captured various aspects of the tumor advancement like gap formation, buds and spikes formation, island and cavity formation in the stromal region, and up to some extent even INFb and INFc infiltrative growth patterns were observed. Such vast coverage of invasive features was possible, on the one hand, due to the highly nonlinear coupling via GGR functions and the flux modulation function J and on the other hand the noisy perturbations could bring about different variations in the patterns. Moreover, the model also highlighted that spatial perturbations/unevenness/heterogeneity in structural density of the stroma have a strong influence on the invasion patterns. Hence, it is expected that the range of possible INF patters would be enlarged if one were to incorporate spatial noise both in proton and normal cell dynamics.

Aknowledgement

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Figure 14: Time snapshots of the sample solution number 5, in the case of a 2D domain.

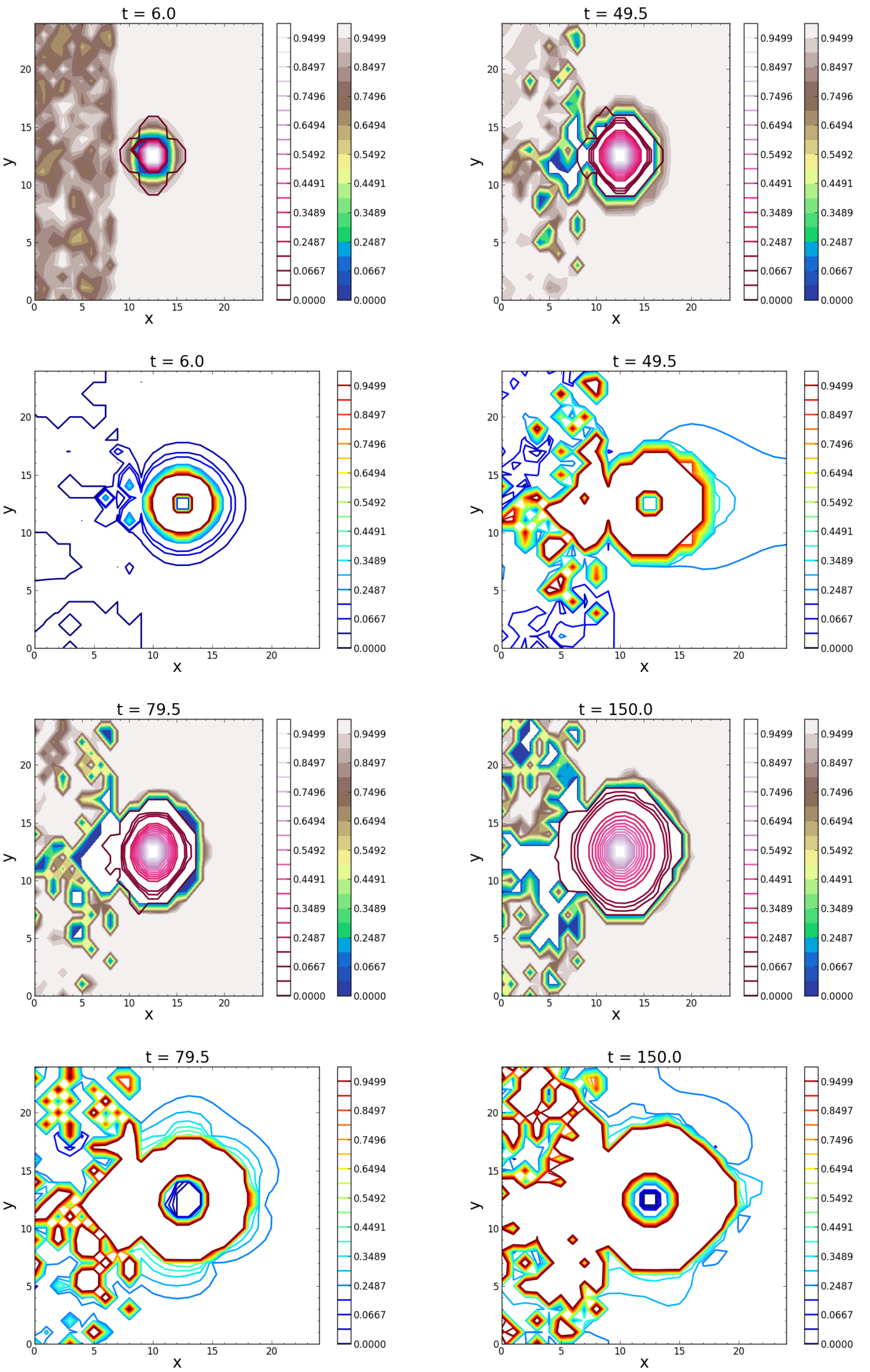


Figure 15: Time snapshots of the sample solution number 25, in the case of a 2D domain.

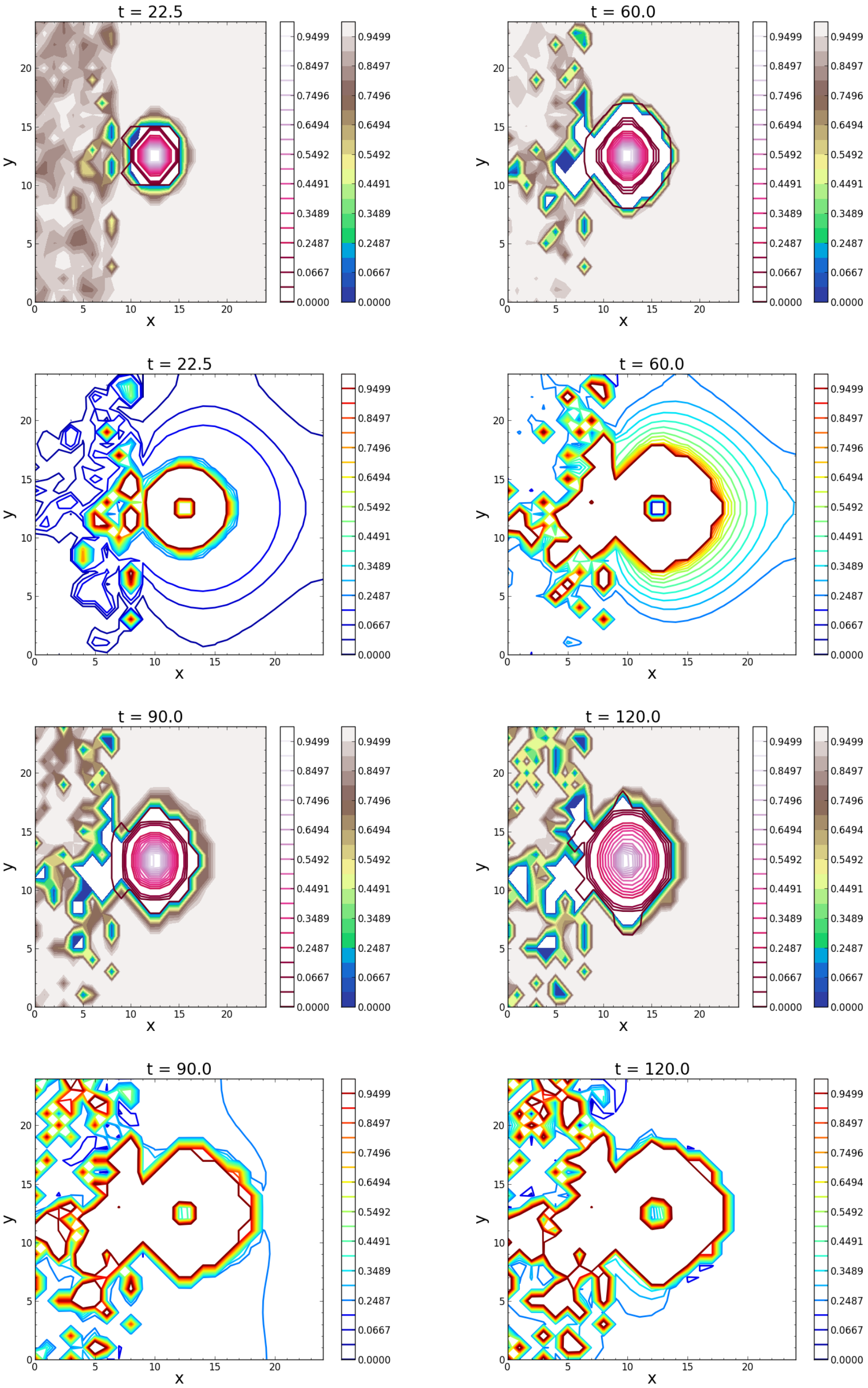


Figure 16: Time snapshots of the sample solution number 100, in the case of a 2D domain.

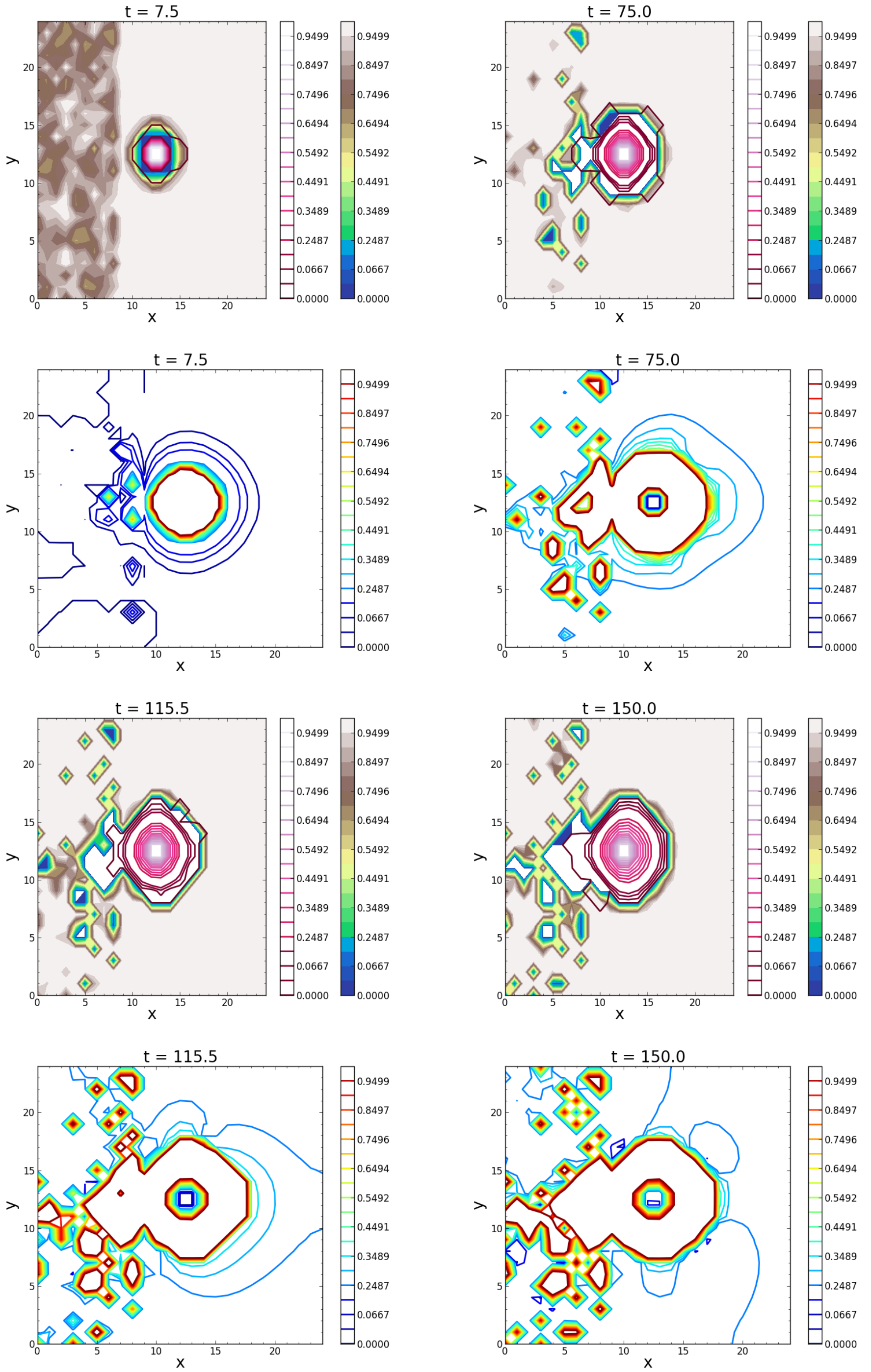


Figure 17: Time snapshots of the sample solution number 49, in the case of a 2D domain.

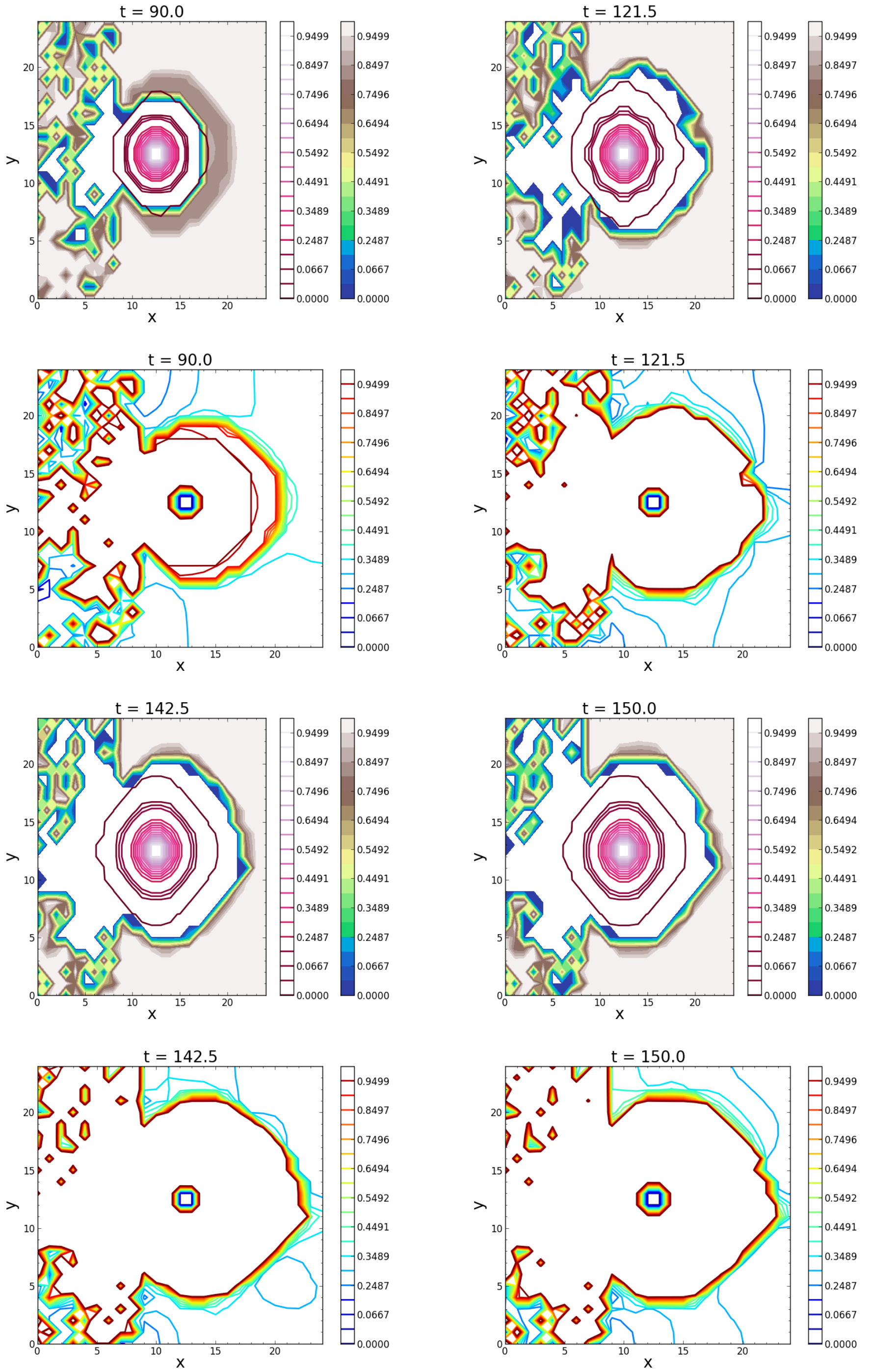
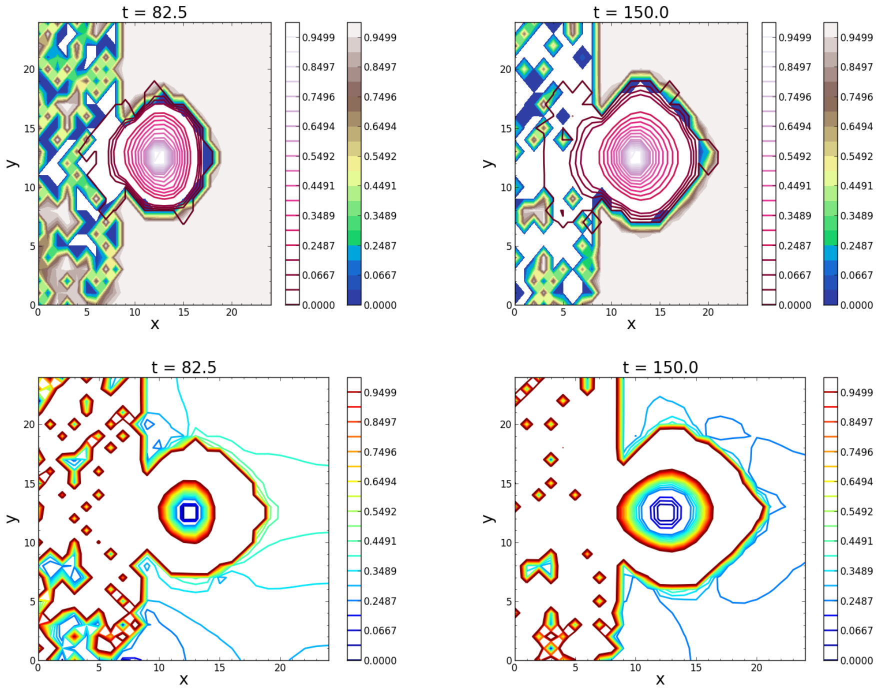


Figure 18: Simulation plots for $\gamma_{\Lambda_3} = .3144$, $\gamma_b = .8512$ and $\gamma_{\Lambda_4} = 32$.

(a) Sample solution number 2



(b) Sample solution number 3

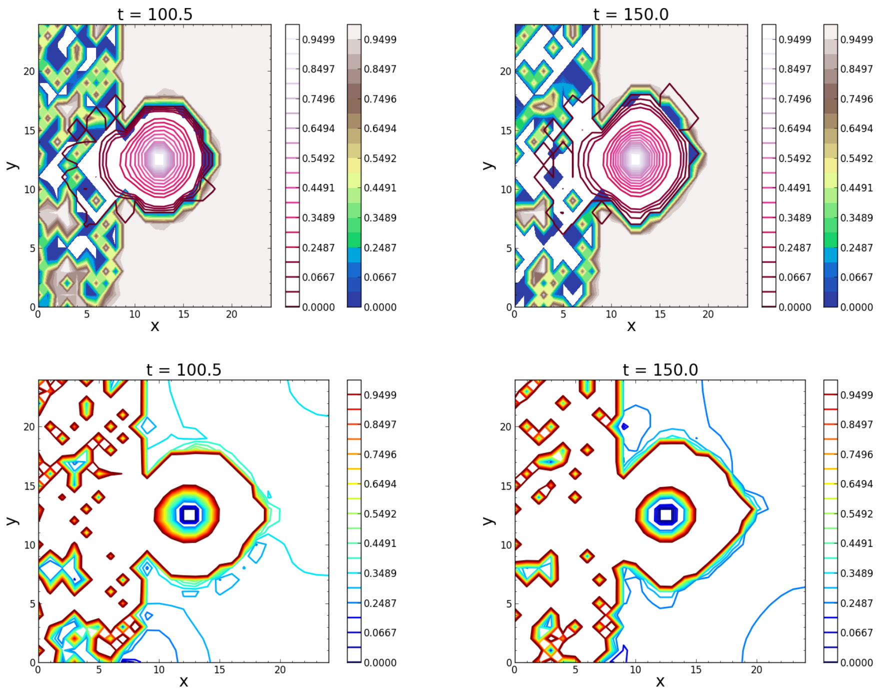


Figure 19: Time snapshots of the expected value of sample solutions.

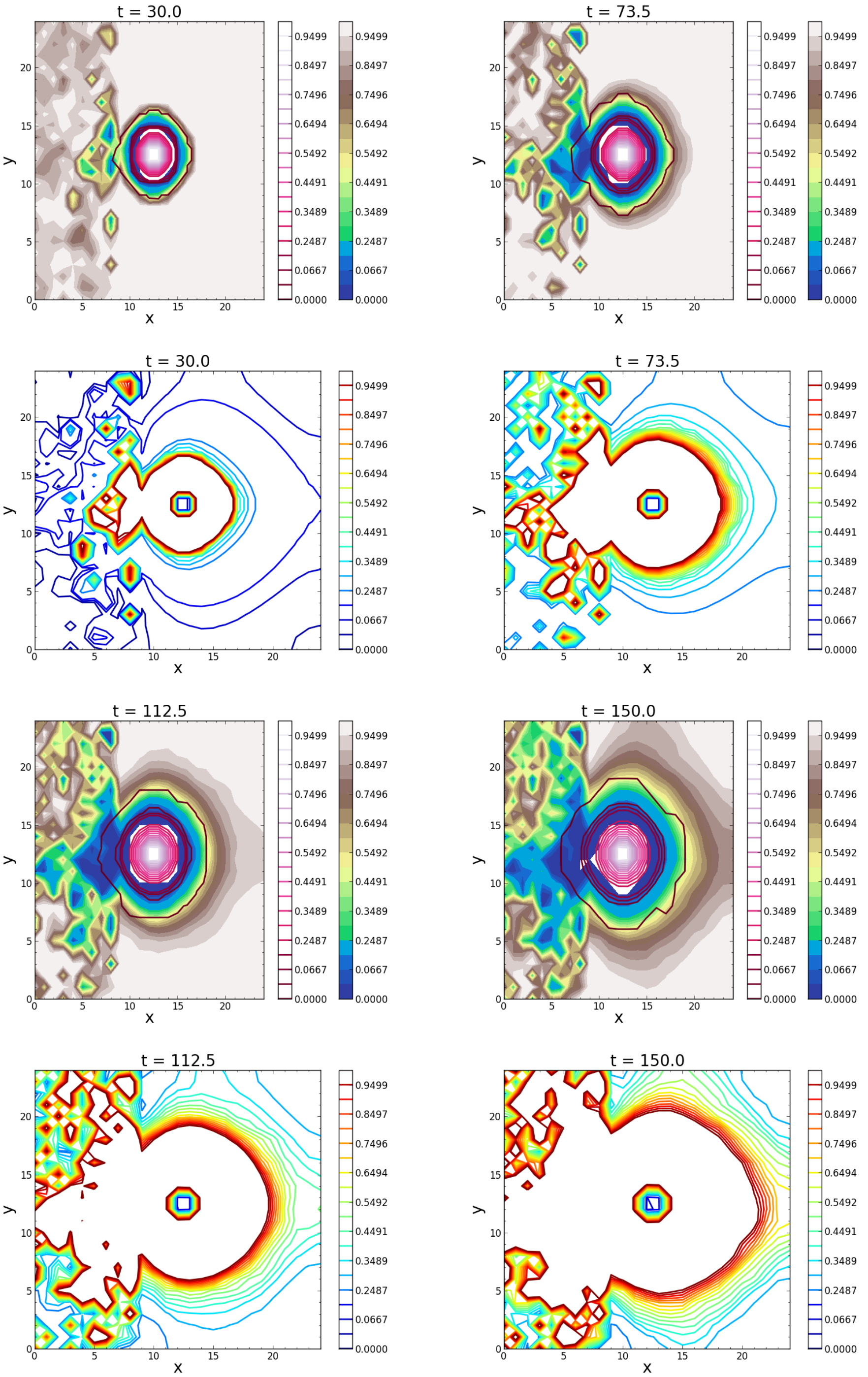


Figure 20: Time snapshots of the expected values of sample solutions for $\gamma_{\Lambda_3} = 2.4144$. Unlike in Figure 19, here the gap is visible (e.g. at time T=112.5) even in expectation.

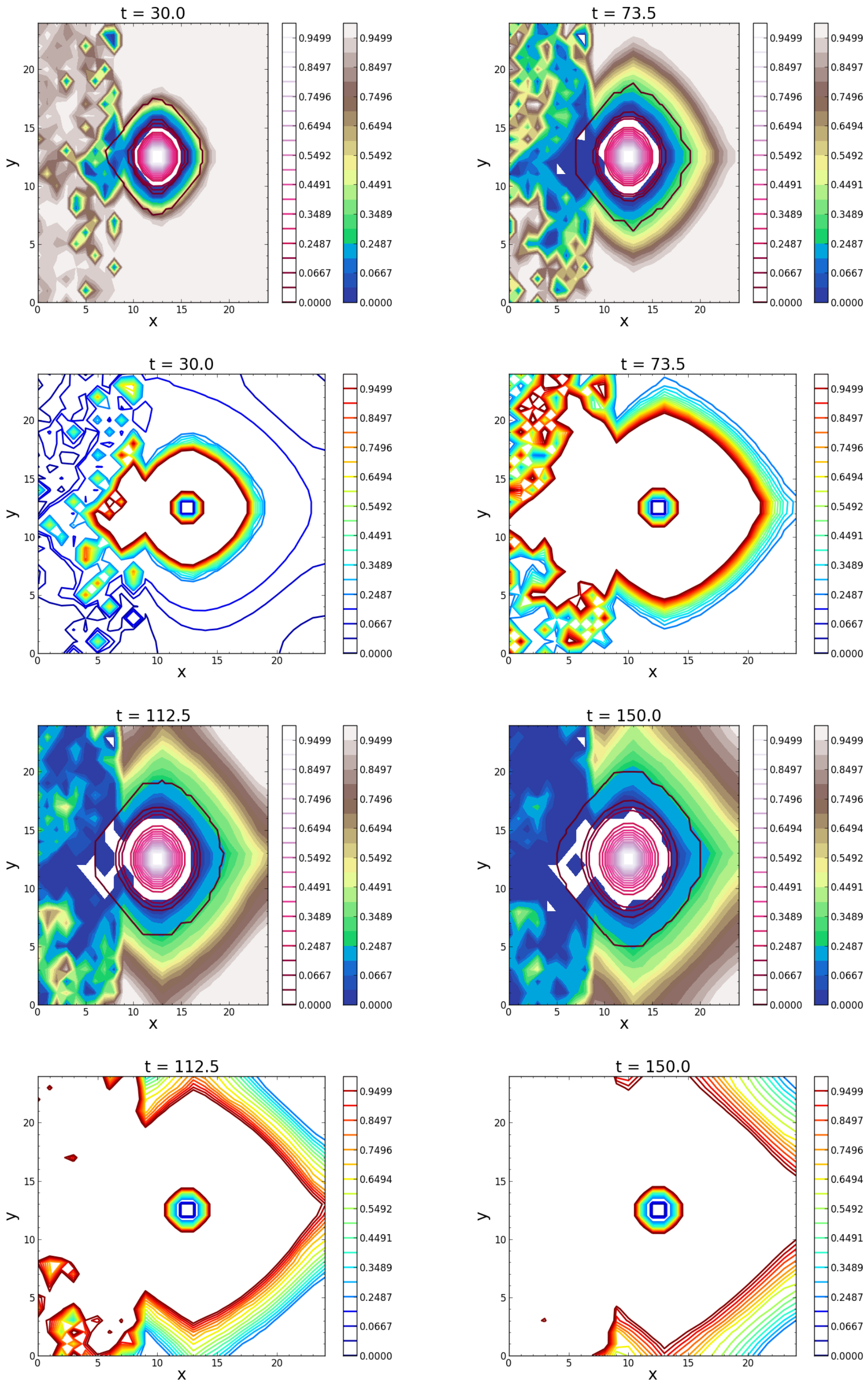


Table 2: Model parameters

Growth and decay parameters Ξ_R			
	Phenomenological relevance	1D	2D
γ_N	decay of normal cells due to non-acid related byproducts	5	5
γ_{Λ_1}	decay of cancer cells due to non-physiological intracellular acid levels	.004	.004
γ_{Λ_2}	growth of cancer cells due to favorable intracellular acid levels	.00001	.00001
γ_{Λ_3}	growth of normal cells due to acid induced immune response	.6144	.8144
γ_{Λ_4}	decay of normal cells due to extracellular acid levels	8	8
$\gamma_{\Lambda_{4,1}}$	decay of normal cells due to extracellular alkalinity	0	500
γ_ξ	intensity of noise for the intracellular proton dynamics	3	3
K_C	carrying capacity of cancer cells	-	-
K_N	carrying capacity of normal cells	-	-

Migration parameters Ξ_M			
	Phenomenological relevance	1D	2D
γ_D	apparent diffusion coefficient of protons	.0035	.0001
γ_g	coefficient for repulsion of protons away from cancer cells	.0021	.0001
γ_h	coefficient for repulsion of protons away from normal cells	.0021	.0001
γ_a	diffusion coefficient for cancer cells	.00006	.0000099
γ_b	speed of advection for cancer cells	.0046	.0542

7 Appendix

7.1 Non-dimensionalization:

Let $\tau := 10^{-7}$ (measured in min) be a time normalizing constant and $K_w := 10^{-7}$ (measured in $\frac{M}{vol}$) be the molar concentration of protons in water per unit vol. Let the dependent variables H_i and H_e (both measured in $\frac{M}{vol}$) be represented in a non-dimensional form as $\overline{H}_i := \frac{H_i}{K_w}, \overline{H}_e := \frac{H_e}{K_w}$. Similarly, the time variable t (measured in min) and spatial variable x (measured in $dist$[5]) are non-dimensionalized as $\bar{t} = \frac{t}{\tau}, \overline{x} = \frac{x}{\sqrt{D\tau}}$, where D (measured in $\frac{dist^2}{min}$) is a normalizing constant for the diffusion coefficient of extracellular protons.

Let K_C and K_N be the carrying capacities of cancer cell density C and normal cell density N, respectively. Then the non-dimensional formulation can be deduced using the following rescaling relations:

$$\left.\begin{array}{lll}
\overline{T}_1 := \frac{\tau}{K_w}T_1, & \overline{T}_2 := \frac{\tau}{K_w}T_2, & \overline{T}_3 := \frac{\tau}{K_w}T_3,\\
\overline{q}_1 := \frac{\tau}{K_w}q_1, & \overline{q}_2 := \tau q_2, & \overline{Q} := \frac{\tau}{K_w}Q,\\
\overline{\Delta} := D\tau\Delta, & \frac{\tau}{K_w} := 1, & \bar{t} := \frac{t}{\tau},\\
\overline{\gamma}_g := \frac{K_C}{K_w D}\gamma_g, & \overline{\gamma}_h := \frac{K_N}{K_w D}\gamma_h, & \overline{\gamma}_{\Lambda_1} := \tau\gamma_{\Lambda_1},\\
\overline{\gamma}_{\Lambda_2} := \tau\gamma_{\Lambda_2}, & \overline{\gamma}_a := \frac{\gamma_a}{D}, & \overline{\gamma}_b := \frac{\gamma_b}{D},\\
\overline{\gamma}_{\Lambda_3} := \tau\gamma_{\Lambda_3}, & \overline{\gamma}_{\Lambda_4} := \tau\gamma_{\Lambda_4}, & \overline{\gamma}_{\Lambda_{4,1}} := \gamma_{\Lambda_{4,1}},\\
\overline{C} := \frac{C}{K_C}, & \overline{N} := \frac{N}{K_N}. &
\end{array}\right\} \tag{71}$$

7.2 Concentration inequality

Theorem 7.1. *Let $Y_t \sim \mathcal{N}(0, \sigma_t^2)$, $t \in [0,T]$, $T < \infty$, be a real-valued Gaussian process. Let ρ_T be the median of $\sup_{t\in[0,T]} Y_t$ and $\mathrm{k}_{\sigma_T} := \sup_{t\in[0,T]} \sigma_t < \infty$. Then for all $t > 0$, we have*

$$\begin{aligned}
\mathbb{P}\Big(|\sup_{t\in[0,T]} Y_t - \rho_T| \geq \mathrm{k}_{\sigma_T} t\Big) &\leq \frac{2}{\sqrt{2\pi}}\int_t^\infty \mathrm{e}^{-\frac{x^2}{2}}\,dx,\\
\mathbb{P}\Big(|\sup_{t\in[0,T]} |Y_t| - \rho_T| \geq \mathrm{k}_{\sigma_T} t\Big) &\leq \frac{3}{\sqrt{2\pi}}\int_t^\infty \mathrm{e}^{-\frac{x^2}{2}}\,dx.
\end{aligned} \tag{72}$$

Moreover, the median ρ_T is unique.

[5] $dist$ refers to some unit of distance suitable for the macroscopic scale of tissues

Proof. Theorem 5.4.3 and Remark 5.4.4 from [28, pp. 219, 224]. ∎

Corollary 2. *Let Y_t, ρ_T, k_{σ_T} be as in Theorem 7.1. Then for $T<\infty$, the following inequality holds:*

$$\mathbb{E}[|\sup_{t\in[0,T]}|Y_t|-\rho_T|^i]\leq\frac{3}{2\sqrt{\pi}}\mathrm{k}_{\sigma_T}^i2^{\frac{i}{2}}\Gamma\Big(\frac{i+1}{2}\Big),\ \textit{for all } i\in\mathbb{N},\tag{73}$$

where Γ denotes the usual gamma function defined by way of the Euler integral of the second kind

Proof. Let the random variable Z_T be defined as

$$Z_T:=\frac{\sup_{t\in[0,T]}|Y_t|-\rho_T}{\mathrm{k}_{\sigma_T}},$$

then, using the estimate (72), we get

$$\begin{aligned}\mathbb{E}[|Z_T|^i]&=\int_0^\infty\mathbb{P}\Big(|Z_T|^i\geq t\Big)dt\leq\int_0^\infty\mathbb{P}\Big(|Z_T|\geq t^{\frac{1}{i}}\Big)dt=\int_0^\infty\mathbb{P}\Big(|Z_T|\geq s\Big)ds^i,\quad (s:=t^{1/i})\\&\leq\frac{3}{\sqrt{2\pi}}\int_0^\infty\int_s^\infty\mathrm{e}^{-\frac{r^2}{2}}drds^i=\frac{3}{\sqrt{2\pi}}\int_0^\infty s^i\mathrm{e}^{-\frac{s^2}{2}}ds=\frac{3}{\sqrt{2\pi}}\int_0^\infty2^{\frac{i-1}{2}}t^{\frac{i+1}{2}-1}\mathrm{e}^{-t}dt\\&=\frac{3}{2\sqrt{\pi}}2^{\frac{i}{2}}\Gamma\Big(\frac{i+1}{2}\Big).\end{aligned}$$

Multiplying both sides by $\mathrm{k}_{\sigma_T}^i$ we arrive at the claim. ∎

Lemma 7.2.

$$\frac{2^{\frac{k}{2}}\Gamma\Big(\frac{k+1}{2}\Big)}{k!}\leq\begin{cases}\frac{\sqrt{\pi}\,2^{-\frac{k}{2}}}{(\frac{k}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is even,}\\ \frac{\sqrt{2}\,2^{-\frac{k-1}{2}}}{(\frac{k-1}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is odd.}\end{cases}\tag{74}$$

$$\frac{2^{\frac{k+2}{2}}\Gamma\Big(\frac{k+3}{2}\Big)}{k!}\leq\begin{cases}\frac{\sqrt{2\pi}}{(\frac{k}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is even,}\\ \frac{2\sqrt{2}}{(\frac{k-1}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is odd.}\end{cases}\tag{75}$$

$$\frac{2^{\frac{k+4}{2}}\Gamma\Big(\frac{k+5}{2}\Big)}{k!}\leq\begin{cases}\frac{4\cdot2^{\frac{k}{2}}\sqrt{\pi}}{(\frac{k}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is even,}\\ \frac{4\cdot2^{\frac{k-1}{2}}2\sqrt{2}}{(\frac{k-1}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is odd.}\end{cases}\tag{76}$$

$$\frac{2^{\frac{k+6}{2}}\Gamma\Big(\frac{k+7}{2}\Big)}{k!}\leq\begin{cases}\frac{16\cdot2^k\sqrt{2\pi}}{(\frac{k}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is even,}\\ \frac{32\cdot2^{\frac{2(k-1)}{2}}2\sqrt{2}}{(\frac{k-1}{2})!} & \textit{if } k\in\mathbb{N} \textit{ is odd.}\end{cases}\tag{77}$$

Proof.
1. **k = 0:** For $k=0$ we have that $\Gamma(\frac{1}{2})=\sqrt{\pi}$, thus the claim is valid.
2. **k = 1:** For $k=1$ we have that $\sqrt{2}\Gamma(1)=\sqrt{2}$, so the claim is valid, too.
3. $k>1$ **and** k **even:**

$$\begin{aligned}\frac{2^{\frac{k}{2}}\Gamma(\frac{k+1}{2})}{k!}&=\frac{2^{\frac{k}{2}}\overbrace{(\frac{k+1}{2}-1)(\frac{k+1}{2}-2)(\frac{k+1}{2}-3)\dots(\frac{k+1}{2}-\frac{k}{2})}^{\frac{k}{2}\text{ terms}}\Gamma(\frac{1}{2})}{k(k-1)(k-2)(k-3)(k-4)(k-5)\dots6\,5\,4\,3\,2\,1}\\&=\frac{2^{\frac{k}{2}}(\frac{k-1}{2})(\frac{k-3}{2})(\frac{k-5}{2})\dots(\frac{1}{2})\Gamma(\frac{1}{2})}{k(k-1)(k-2)(k-3)(k-4)(k-5)\dots6\,5\,4\,3\,2\,1}\\&=\frac{\Gamma(\frac{1}{2})}{k(k-2)(k-4)(k-6)\dots6\,4\,2\,1}\\&=\frac{\sqrt{\pi}}{2^{\frac{k}{2}}(\frac{k}{2})(\frac{k}{2}-1)(\frac{k}{2}-2)(\frac{k}{2}-3)\dots4\,3\,2\,1}\\&=\frac{2^{-\frac{k}{2}}\sqrt{\pi}}{(\frac{k}{2})(\frac{k}{2}-1)(\frac{k}{2}-2)(\frac{k}{2}-3)\dots4\,3\,2\,1}=\frac{2^{-\frac{k}{2}}\sqrt{\pi}}{(\frac{k}{2})!}.\end{aligned}$$

4. $k > 1$ **and** k **odd:** Let $k := 2n+1$,

$$
\begin{aligned}
\frac{2^{\frac{k}{2}}\Gamma(\frac{k+1}{2})}{k!} &= \frac{2^{\frac{k}{2}}\overbrace{(\frac{k+1}{2}-1)(\frac{k+1}{2}-2)(\frac{k+1}{2}-3)\dots(\frac{k+1}{2}-\frac{k-1}{2}))}^{n \text{ terms}}}{k(k-1)(k-2)(k-3)(k-4)(k-5)\dots 6\,5\,4\,3\,2\,1} \\
&= \frac{2^{\frac{k}{2}}(\frac{k-1}{2})(\frac{k-3}{2})(\frac{k-5}{2})\dots(\frac{4}{2})(\frac{2}{2})}{k(k-1)(k-2)(k-3)(k-4)(k-5)\dots 6\,5\,4\,3\,2\,1} \\
&= \frac{\sqrt{2}}{k(k-2)(k-4)\dots 7\,5\,3\,1} \\
&= \frac{\sqrt{2}}{(2n+1)(2n-1)(2n-3)(2n-5)\dots 7\,5\,3\,1} \\
&= \frac{\sqrt{2}}{2^{\frac{k-1}{2}}(n+\frac{1}{2})(n-\frac{1}{2})(n-\frac{3}{2})\dots(\frac{7}{2})(\frac{5}{2})(\frac{3}{2})1} \\
&< \frac{2^{\frac{-(k-1)}{2}}\sqrt{2}}{(n)(n-1)(n-2)\dots 3\,2\,1} = \frac{2^{\frac{-(k-1)}{2}}\sqrt{2}}{(\frac{k-1}{2})!}.
\end{aligned}
$$

This establishes the estimate (74). The estimate (75) is obtained by observing that $k \le 2^{\frac{k}{2}}$ for $k \ge 4$ and

$$2^{\frac{k+2}{2}}\,\Gamma\Big(\frac{k+3}{2}\Big) = (k+1)2^{\frac{k}{2}}\Gamma\Big(\frac{k+1}{2}\Big).$$

Similarly,

$$2^{\frac{k+4}{2}}\,\Gamma\Big(\frac{k+5}{2}\Big) = (k+3)(k+1)2^{\frac{k}{2}}\Gamma\Big(\frac{k+1}{2}\Big).$$

$$2^{\frac{k+6}{2}}\,\Gamma\Big(\frac{k+7}{2}\Big) = (k+5)(k+3)(k+1)2^{\frac{k}{2}}\Gamma\Big(\frac{k+1}{2}\Big).$$

■

Lemma 7.3. *Let X be a Banach space. Let $\xi_t \sim \mathcal{N}(\mu_t, \sigma_t^2)$ be a Gaussian process with $\sigma_t > \epsilon > 0$ for all $t \ge 0$. Then for $t, s \ge 0$, $s \ne t$ and $T < \infty$ fixed*

$$\mathbb{E}\Big[\Big(\sup_{\substack{t,s\in[0,T]\\ s<t}} \|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X\Big)^2\Big] \le \mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}^2_{\xi_T}} < \infty, \tag{78}$$

$$\mathbb{E}\Big[\Big(\sup_{\substack{t,s\in[0,T]\\ s<t}} \frac{\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X}{|t-s|}\Big)^2\Big] \le \mathrm{k}_{\xi_{2,T}}\mathrm{e}^{4\mathrm{k}^2_{\xi_{2,T}}} < \infty, \tag{79}$$

with appropriately chosen constants $\mathrm{k}^2_{\xi_T}$ and $\mathrm{k}_{\xi_{2,T}}$.

Proof. For $\xi_t \sim \mu_t + Y_t$ with $Y_t \sim \mathcal{N}(0,\sigma_t^2)$ and with $Z_T := \sup_{t\in[0,T]} |Y_t|$ we use (73) to obtain that

$$\mathbb{E}[(\sup_{t\in[0,T]}|\xi_t|)^i] \le \mathrm{k}^i_{\mu_T} + \mathbb{E}[Z_T^i] \le \mathrm{k}^i_{\mu_T} + \rho_T^i + \frac{3}{2\sqrt{\pi}}\mathrm{k}^i_{\sigma_T}2^{i/2}\Gamma\Big(\frac{i+1}{2}\Big).$$

Next observe that

$$\|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X \le \mathrm{e}^{\int_s^t \|A_1(r)\|dr} \le \mathrm{e}^{\int_s^t \|J(C)\xi_r\|dr} \le \mathrm{e}^{\mathrm{M}_J\int_s^t |\xi_r|dr}, \tag{80}$$

where $\mathrm{M}_J := \mathrm{M}_J(\mathrm{k}_C)$ is the constant in Subsection 3.1 introduced as an upper bound of $J(C)$.

$$\|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X \le \mathrm{e}^{\mathrm{M}_J\int_s^t |\xi_r|dr} = \sum_{i=0}^{\infty}\frac{1}{i!}\Big(\mathrm{M}_J\int_s^t|\xi_r|dr\Big)^i \le \sum_{i=0}^{\infty}\frac{1}{i!}\mathrm{M}_J^iT^i\sup_{r\in[0,T]}|\xi_r|^i.$$

Hence,

$$\mathbb{E}\Big[\Big(\sup_{t,s\in[0,T]}\|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X\Big)^2\Big] \le \sum_{i=0}^{\infty}\frac{2^i\,\mathrm{M}_J^i T^i}{i!}\mathbb{E}(\sup_{r\in[0,T]}|\xi_r|^i)$$
$$\le \sum_{i=0}^{\infty}\frac{2^i\,\mathrm{M}_J^i T^i}{i!}\Big(\mathrm{k}_{\mu_T}^i+\rho_T^i+3\mathrm{k}_{\sigma_T}^i 2^{\frac{i}{2}}\,\Gamma\Big(\frac{i+1}{2}\Big)\Big)$$
$$\le \sum_{i=0}^{\infty}2^i\frac{1}{i!}\mathrm{M}_J^i T^i\hat{\mathrm{k}}_{\xi_T}^i 2^{\frac{i}{2}}\,\Gamma\Big(\frac{i+1}{2}\Big), \tag{81}$$

where we used the recurrence $\Gamma(s+1)=s\Gamma(s)$ (for s positive) and the notations

$$\mathrm{k}_{\sigma_T} := \sup_{r\in[0,T]}\sigma(r),\quad \hat{\mathrm{k}}_{\xi_T}^i := \mathrm{M}_J^i T^i(\mathrm{k}_{\mu_T}^i+\rho_T^i+3\mathrm{k}_{\sigma_T}^i),$$
$$\mathrm{k}_{\mu_T} := \sup_{t\in[0,T]}\mu_t,\qquad \mathrm{k}_{\rho_T} := \mathrm{Median}\Big(\sup_{t\in[0,T]}Y_t\Big).$$

Using estimate (74) in (81) we get that

$$\sum_{i=0}^{\infty}2^i\frac{1}{i!}2^{\frac{i}{2}}\hat{\mathrm{k}}_{\xi_T}^i\,\Gamma\Big(\frac{i+1}{2}\Big) = \sum_{\substack{i=0\\ i\text{ even}}}^{\infty}\hat{\mathrm{k}}_{\xi_T}^i\frac{2^i\,2^{\frac{i}{2}}\Gamma(\frac{i+1}{2})}{i!}+\hat{\mathrm{k}}_{\xi_T}^{i+1}\frac{2^{i+1}\,2^{\frac{i+1}{2}}\Gamma(\frac{i+2}{2})}{(i+1)!}$$
$$\le \sum_{\substack{i=0\\ i\text{ even}}}^{\infty}\hat{\mathrm{k}}_{\xi_T}^i\frac{2^i\sqrt{\pi}}{2^{\frac{i}{2}}(\frac{i}{2})!}+\hat{\mathrm{k}}_{\xi_T}^{i+1}\frac{2^{i+1}\sqrt{2}}{2^{\frac{i}{2}}(\frac{i}{2})!}$$
$$\le \sqrt{\pi}(1+2\hat{\mathrm{k}}_{\xi_T})\sum_{\substack{i=0\\ i\text{ even}}}^{\infty}\frac{\hat{\mathrm{k}}_{\xi_T}^i 2^{\frac{i}{2}}}{(\frac{i}{2})!}=\sqrt{\pi}(1+2\hat{\mathrm{k}}_{\xi_T})\sum_{i=0}^{\infty}\frac{\hat{\mathrm{k}}_{\xi_T}^{2i}2^i}{i!}=\mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}_{\xi_T}^2}.$$

Altogether, we have that

$$\mathbb{E}\Big[\Big(\sup_{t,s\in[0,T]}\|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X\Big)^2\Big]\le \mathrm{k}_{\xi_T}\mathrm{e}^{2\mathrm{k}_{\xi_T}^2},$$
$$\Bigg(\mathbb{E}\Big[\Big(\sup_{t,s\in[0,T]}\|\mathrm{e}^{\int_s^t A_1(r)dr}\|_X\Big)^2\Big]\Bigg)^{\frac{1}{2}}\le \sqrt{\mathrm{k}_{\xi_T}}\mathrm{e}^{\mathrm{k}_{\xi_T}^2}.$$

The second estimate follows similarly:

$$\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X=\sum_{i=0}^{\infty}\frac{1}{(i+1)!}\Big(\mathrm{M}_J\int_s^t|\xi_r|dr\Big)^{i+1}\le\sum_{i=0}^{\infty}\frac{1}{(i+1)!}\Big(\mathrm{M}_J\int_s^t\sup_{r\in[0,T]}|\xi_r|dr\Big)^{i+1}$$
$$\le \mathrm{M}_J|t-s|\sum_{i=0}^{\infty}\frac{1}{i!}\mathrm{M}_J^i T^i\sup_{r\in[0,T]}|\xi_r|^{i+1},$$
$$\Rightarrow \sup_{t,s\in[0,T]}\frac{\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X}{|t-s|}\le \mathrm{M}_J\sum_{i=0}^{\infty}\frac{1}{i!}\mathrm{M}_J^i T^i\sup_{r\in[0,T]}|\xi_r|^{i+1}.$$

Therefore,

$$\Big(\sup_{t,s\in[0,T]}\frac{\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X}{|t-s|}\Big)^2\le \mathrm{k}_{C_{p1}}^2\sum_{i=0}^{\infty}2^i\frac{1}{i!}\mathrm{M}_J^i T^i\sup_{r\in[0,T]}|\xi_r|^{i+2}.$$

Hence,

$$\mathbb{E}\Big[\Big(\sup_{t,s\in[0,T]}\frac{\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X}{|t-s|}\Big)^2\Big]\le\sum_{i=0}^{\infty}\frac{2^i\,\mathrm{k}_{C_{p1}}^{i+2}T^i}{i!}\mathbb{E}\Big(\sup_{r\in[0,T]}|\xi_r|\Big)^{i+2}$$
$$\le\sum_{i=0}^{\infty}\frac{2^i\,\mathrm{k}_{C_{p1}}^{i+2}T^i}{i!}\Big(\mathrm{k}_{\mu_T}^{i+2}+\rho_T^{i+2}+3\mathrm{k}_{\sigma_T}^{i+2}\,2^{\frac{i+2}{2}}\Gamma\Big(\frac{i+3}{2}\Big)\Big)$$
$$\le\sum_{i=0}^{\infty}\frac{2^i\,\mathrm{k}_{C_{p1}}^{i+2}T^i}{i!}\Big(\mathrm{k}_{\mu_T}^{i+2}+\rho_T^{i+2}+3\mathrm{k}_{\sigma_T}^{i+2}\Big)\,2^{\frac{i+2}{2}}\Gamma\Big(\frac{i+3}{2}\Big)$$
$$\le\sum_{i=0}^{\infty}2^i\hat{\mathrm{k}}_{\xi_{2,T}}^{i+2}\frac{2^{\frac{i+2}{2}}\Gamma\Big(\frac{i+3}{2}\Big)}{i!}, \tag{82}$$

where $\hat{\mathrm{k}}_{\xi_{2,T}}^{i+2} := (1+\mathrm{M}_J)^{i+2}(1+T)^{i+2}(\mathrm{k}_{\mu_T}^{i+2}+\rho_T^{i+2}+3\mathrm{k}_{\sigma_T}^{i+2})$ and $\mathrm{k}_{C_{p1}} := \mathrm{M}_J+1$. Using estimate (75) in (82) analogously as above we get that

$$\sum_{i=0}^{\infty} 2^i \hat{\mathrm{k}}_{\xi_{2,T}}^{i+2} \frac{2^{\frac{i+2}{2}}\Gamma\Big(\frac{i+3}{2}\Big)}{i!} = \hat{\mathrm{k}}_{\xi_{2,T}}^2 2\sqrt{2}(1+2\hat{\mathrm{k}}_{\xi_{2,T}}) \sum_{i=0}^{\infty} \frac{\hat{\mathrm{k}}_{\xi_T}^{2i} 2^{2i}}{i!} = \mathrm{k}_{\xi_{2,T}} \mathrm{e}^{4\mathrm{k}_{\xi_{2,T}}^2}.$$

Altogether we have that

$$\mathbb{E}\Big[\Big(\sup_{t,s\in[0,T]} \frac{\|\mathrm{e}^{\int_s^t A_1(r)dr}-1\|_X}{|t-s|}\Big)^2\Big] \leq \mathrm{k}_{\xi_{2,T}} \mathrm{e}^{4\mathrm{k}_{\xi_{2,T}}^2}.$$

■

Remark 2. *Under the conditions of Lemma 7.3, we also obtain*

$$\mathbb{E}(\Big\||\xi_t|\,\mathrm{e}^{\int_s^t A_1(r)}\Big\|_{B_X}^2) \leq \mathrm{k}_{\xi_T}\mathrm{e}^{4\mathrm{k}_{\xi_T}^2} < \infty, \tag{83}$$

$$\mathbb{E}(\Big\||\xi_t|[\mathrm{e}^{\int_s^t A_1(r)}-1]\Big\|_{B_X}^2) \leq |t-s|^2\mathrm{k}_{\xi_{2,T}}\mathrm{e}^{8\mathrm{k}_{\xi_{2,T}}^2} < \infty, \tag{84}$$

with constants k_{ξ_T} and $\mathrm{k}_{\xi_{2,T}}$ possibly differing from the respective ones in Lemma 7.3.

Lemma 7.4. *Let Y be a Banach space and $(\xi_t)_{t\geq 0}$ be an $(\mathcal{A}_t)_{t\geq 0}$-adapted Gaussian process with independent increments, i.e. for $t>s\geq r\geq 0$, $\sigma(\xi_t-\xi_s)$ is independent of $\mathcal{A}_r$. Then for an $(\mathcal{A}_t)_{t\geq 0}$-adapted process $(u_t)_{t\geq 0}$ given by*

$$u_t^1 = e^{\int_{t_1}^t J_s\xi_s ds}u_{t_1}^1 + \int_{t_1}^t e^{\int_s^t J_r\xi_r dr} r_s^1 ds, \quad \textit{for} \quad t\in[t_1,T_1], \textit{ and}$$

$$u_t^1 = e^{\int_{t_0}^t J_s\xi_s ds}u_{t_0}^1 + \int_{t_0}^t e^{\int_s^t J_r\xi_r dr} r_s^1 ds, \quad \textit{for} \quad t\in[t_0,t_1],$$

we have that

$$\mathbb{E}\Bigg[\Big(\sup_{t_2\in[t_1,T_1]} \mathrm{e}^{\int_{t_1}^{t_2}\|A_1(s)\|_Y ds}\|u_{t_1}^1\|_Y\Big)^2\Bigg] \leq \mathrm{k}_{suf}\mathrm{e}^{\mathrm{k}_{suf}\mathrm{k}_{\xi_{2,T_1}}^2}\Big(\mathbb{E}[\|u_{t_0}^1\|_Y^2]+\mathbb{E}[\|u_{t_1}^1\|_{B_Y}^2]+\mathbb{E}[\|r^1\|_{B_Y}^2]\Big),$$

and

$$\mathbb{E}\Bigg[\Big(\sup_{t_2\in[t_1,T_1]} \Big|\mathrm{e}^{\int_{t_1}^{t_2}\|A_1(s)\|_Y ds}-1\Big|\|u_{t_1}^1\|\Big)^2\Bigg] \leq |t_1-t_2|^2\mathrm{k}_{suf}\mathrm{e}^{\mathrm{k}_{suf}\mathrm{k}_{\xi_{2,T_1}}^2}\Big(\mathbb{E}[\|u_{t_0}^1\|_Y^2]+\mathbb{E}[\|u_{t_1}^1\|_{B_Y}^2]+\mathbb{E}[\|r^1\|_{B_Y}^2]\Big).$$

Proof. Since $\phi(x) := |x|^k$ is a convex function for $k\geq 1$, by Jensen's inequality we get

$$\begin{aligned}
\phi\Big(\int_{t_1}^{t_2}\xi_s ds\Big)\|u_{t_1}^1\|_Y^2 &\leq \Big(\frac{1}{t_2-t_1}\int_{t_1}^{t_2}\phi((t_2-t_1)\xi_s)ds\Big)\|u_{t_1}^1\|_Y^2 = (t_2-t_1)^{k-1}\Big(\int_{t_1}^{t_2}|\xi_s|^k ds\Big)\|u_{t_1}^1\|_Y^2\\
&\leq 2^k(t_2-t_1)^{k-1}\Big(\int_{t_1}^{t_2}|\xi_s-\xi_{t_1}|^k ds\Big)\|u_{t_1}^1\|_Y^2 + 2^k(t_2-t_1)^k|\xi_{t_1}|^k\|u_{t_1}^1\|_Y^2\\
&\leq \mathrm{Term}_1+\mathrm{Term}_2
\end{aligned}\tag{85}$$

$$\begin{aligned}
\mathrm{Term}_2 &= 2^k(t_2-t_1)^k|\xi_{t_1}|^k\|u_{t_1}^1\|_Y^2\\
&\leq 2^k(t_2-t_1)^k|\xi_{t_1}|^k\Big(\|e^{2\int_{t_0}^{t_1}J_s\xi_s ds}\|\|u_{t_0}^1\|_Y^2 + (t_1-t_0)\int_{t_0}^{t_1}\|e^{2\int_s^{t_1}J_r\xi_r dr}\|\|r_s^1\|_Y^2 ds\Big)\\
&\leq 2^k(t_2-t_1)^k|\xi_{t_1}|^k\left(\sum_{j=0}^{\infty}\frac{1}{j!}\Big(\int_{t_0}^{t_1}2|\xi_s|\mathrm{M}_J ds\Big)^j\|u_{t_0}^1\|_Y^2 + (t_1-t_0)\int_{t_0}^{t_1}\sum_{j=0}^{\infty}\frac{1}{j!}\Big(\int_s^{t_1}2|\xi_r|\mathrm{M}_J dr\Big)^j\|r_s^1\|_Y^2 ds\right)\\
&\leq 4^k(t_2-t_1)^k\left(\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^{j-1}\Big(\int_{t_0}^{t_1}|\xi_{t_1}-\xi_s|^k|\xi_s|^j2^j\mathrm{M}_J^j ds + \int_{t_0}^{t_1}|\xi_s|^k|\xi_s|^j2^j\mathrm{M}_J^j ds\Big)\|u_{t_0}^1\|_Y^2\right.\\
&\left. + (t_1-t_0)\int_{t_0}^{t_1}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^{j-1}\Big(\int_s^{t_1}|\xi_{t_1}-\xi_r|^k|\xi_r|^j2^j\mathrm{M}_J^j dr + \int_s^{t_1}|\xi_r|^k|\xi_r|^j2^j\mathrm{M}_J^j dr\Big)\|r_s^1\|_Y^2 ds\right).
\end{aligned}$$

Taking expectation it follows that

$$\begin{aligned}
\mathbb{E}\left[\Big|\int_{t_1}^{t_2}\xi_s ds\Big|^k \|u_{t_1}^1\|_Y^2\right] &\le 2^k(t_2-t_1)^{k-1}\int_{t_1}^{t_2}\mathbb{E}[|\xi_s-\xi_{t_1}|^k]ds\,\mathbb{E}\|u_{t_1}^1\|_Y^2 + 2^k(t_2-t_1)^k\mathbb{E}[|\xi_{t_1}|^k\|u_{t_1}^1\|_Y^2] \\
&\le 2^k(t_2-t_1)^{k-1}\int_{t_1}^{t_2}\mathbb{E}[|\xi_s-\xi_{t_1}|^k]ds\,\mathbb{E}\|u_{t_1}^1\|_Y^2 \\
&+ 4^k(t_2-t_1)^k\Bigg(\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^{j-1}\Big(\int_{t_0}^{t_1}\mathbb{E}[|\xi_{t_1}-\xi_s|^k]\mathbb{E}[|\xi_s|^j]2^j\mathrm{M}_J^j ds \\
&\qquad + \int_{t_0}^{t_1}\mathbb{E}[|\xi_s|^{k+j}2^j\mathrm{M}_J^j ds\Big)\|u_{t_0}^1\|_Y^2 \\
&+ (t_1-t_0)\int_{t_0}^{t_1}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^{j-1}\Big(\int_s^{t_1}\mathbb{E}[|\xi_{t_1}-\xi_r|^k]\mathbb{E}[|\xi_r|^j]2^j\mathrm{M}_J^j dr \\
&\qquad + \int_s^{t_1}\mathbb{E}[|\xi_r|^{k+j}2^j\mathrm{M}_J^j dr\Big)\|r_s^1\|_Y^2\,ds\Bigg).
\end{aligned}$$

Next we note that

$$\mathbb{E}[|\xi_s-\xi_t|^k] \le \mathbb{E}[(|\xi_s|+|\xi_t|)^k] \le \mathbb{E}[2^k\sup_{t\in[t_1,t_2]}|\xi_s|^k] \le 2^k\mathrm{k}_{\xi_T}^k\Gamma\Big(\frac{k+1}{2}\Big) \tag{86}$$

Using this estimate we get that

$$\begin{aligned}
\mathbb{E}\left[\Big|\int_{t_1}^{t_2}\xi_s ds\Big|^k \|u_{t_1}^1\|_Y^2\right] &\le 2^k(t_2-t_1)^{k-1}\int_{t_1}^{t_2}2^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)ds\mathbb{E}\|u_{t_1}^1\|_Y^2 \\
&+ 4^k(t_2-t_1)^k\Bigg(\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^{j-1}\Big(\int_{t_0}^{t_1}2^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}_{\xi_{T_1}}^j\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}_J^j ds \\
&\qquad + \int_{t_0}^{t_1}\mathrm{k}_{\xi_{T_1}}^j\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}_J^j ds\Big)\mathbb{E}\|u_{t_0}^1\|_Y^2 \\
&+ (t_1-t_0)\int_{t_0}^{t_1}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^{j-1}\Big(\int_s^{t_1}2^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}_{\xi_{T_1}}^j\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}_J^j dr \\
&\qquad + \int_s^{t_1}\mathrm{k}_{\xi_{T_1}}^j\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}_J^j dr\Big)\mathbb{E}[\|r_s^1\|_Y^2]ds\Bigg)
\end{aligned}$$

$$\begin{aligned}
\mathbb{E}\left[\Big|\int_{t_1}^{t_2}\xi_s ds\Big|^k \|u_{t_1}^1\|_Y^2\right] &\le 4^k(t_2-t_1)^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)\mathbb{E}\|u_{t_1}^1\|_Y^2 \\
&+ 4^k(t_2-t_1)^k\Bigg(\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\Big[2^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}_{\xi_{T_1}}^j\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}_J^j \\
&\qquad + \mathrm{k}_{\xi_{T_1}}^j\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}_J^j\Big]\mathbb{E}[\|u_{t_0}^1\|_Y^2] \\
&+ (t_1-t_0)\int_{t_0}^{t_1}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^j\Big[2^k\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}_{\xi_{T_1}}^j\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}_J^j \\
&\qquad + \mathrm{k}_{\xi_{T_1}}^j\mathrm{k}_{\xi_{T_1}}^k\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}_J^j\Big]\mathbb{E}[\|r_s^1\|_Y^2]ds\Bigg)
\end{aligned}$$

$$\mathbb{E}\left[\left|\int_{t_1}^{t_2}\xi_s ds\right|^k \|u^1_{t_1}\|^2_Y\right] \leq 4^k(t_2-t_1)^k \mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\mathbb{E}\|u^1_{t_1}\|^2_Y$$
$$+4^k(t_2-t_1)^k\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\Big[2^k\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}^j_J\Big]\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+4^k(t_2-t_1)^k\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\Big[\mathrm{k}^j_{\xi_{T_1}}\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}^j_J\Big]\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+4^k(t_2-t_1)^k\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^j\Big[2^k\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}^j_J\Big](t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds$$
$$+4^k(t_2-t_1)^k\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-s)^j\Big[\mathrm{k}^j_{\xi_{T_1}}\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}^j_J\Big](t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds,$$

thus

$$\sum_{k=0}^{\infty}\frac{1}{k!}\mathbb{E}\left[\left|\int_{t_1}^{t_2}\xi_s ds\right|^k \|u^1_{t_1}\|^2_Y\right] \leq \sum_{k=0}^{\infty}\frac{1}{k!}4^k(t_2-t_1)^k \mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\mathbb{E}\|u^1_{t_1}\|^2_Y$$
$$+\Big[\sum_{k=0}^{\infty}\frac{1}{k!}8^k(t_2-t_1)^k\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}^j_J\Big]\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\Big[\sum_{k=0}^{\infty}\frac{1}{k!}4^k(t_2-t_1)^k\mathrm{k}^k_{\xi_{T_1}}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}^j_J\Big]\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\Big[\sum_{k=0}^{\infty}\frac{1}{k!}8^k(t_2-t_1)^k\mathrm{k}^k_{\xi_{T_1}}\Gamma\Big(\frac{k+1}{2}\Big)\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+1}{2}\Big)2^j\mathrm{M}^j_J\Big](t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds$$
$$+\Big[\sum_{k=0}^{\infty}\frac{1}{k!}4^k(t_2-t_1)^k\mathrm{k}^k_{\xi_{T_1}}\sum_{j=0}^{\infty}\frac{1}{j!}(t_1-t_0)^j\mathrm{k}^j_{\xi_{T_1}}\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}^j_J\Big](t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds$$

Now using the estimates (74), (75), (76) and (77) and following the lines of the proof of Lemma 7.3, we get

$$\sum_{k=0}^{\infty}\frac{1}{k!}\mathbb{E}\left[\left|\int_{t_1}^{t_2}\xi_s ds\right|^k \|u^1_{t_1}\|^2_Y\right] \leq \mathrm{e}^{4\mathrm{k}^2_{\xi_{T_1}}}\mathbb{E}\|u^1_{t_1}\|^2_Y+\mathrm{e}^{8\mathrm{k}^2_{\xi_{T_1}}+2M_j\mathrm{k}^2_{\xi_{T_1}}}\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\mathrm{e}^{8\mathrm{k}^2_{\xi_{T_1}}+2M_j\mathrm{k}^2_{\xi_{T_1}}}(t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds+\sum_{k=0}^{\infty}\frac{a^k}{k!}\sum_{j=0}^{\infty}\frac{b^j}{j!}\Big[\Gamma\Big(\frac{j+k+1}{2}\Big)\Big]\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\sum_{k=0}^{\infty}\frac{a^k}{k!}\sum_{j=0}^{\infty}\frac{b^j}{j!}\Big[\Gamma\Big(\frac{j+k+1}{2}\Big)2^j\mathrm{M}^j_J\Big](t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds,$$

where $a := 4(t_2-t_1)\mathrm{k}_{\xi_{T_1}}$ and $b := (t_1-t_0)2\mathrm{M}_J\mathrm{k}_{\xi_{T_1}}$. By simplifying the last two terms we finally obtain

$$\sum_{k=0}^{\infty}\frac{1}{k!}\mathbb{E}\left[\left|\int_{t_1}^{t_2}\xi_s ds\right|^k \|u^1_{t_1}\|^2_Y\right] \leq \mathrm{e}^{4\mathrm{k}^2_{\xi_{T_1}}}\mathbb{E}\|u^1_{t_1}\|^2_Y+\mathrm{e}^{(8+2M_j)\mathrm{k}^2_{\xi_{T_1}}}\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\mathrm{e}^{8\mathrm{k}^2_{\xi_{T_1}}+2M_j\mathrm{k}^2_{\xi_{T_1}}}(t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds$$
$$+\mathrm{k}_{suf}\sqrt{\pi}\Big(64_{T_1}\mathrm{M}^2_J\mathrm{k}^2_{\xi_{T_1}}\mathrm{k}^2_{\xi_{T_1}}\Big)\mathrm{e}^{8_{T_1}\mathrm{M}_J\mathrm{k}_{\xi_{T_1}}\mathrm{k}_{\xi_{T_1}}}\mathbb{E}[\|u^1_{t_0}\|^2_Y]$$
$$+\mathrm{k}_{suf}\sqrt{\pi}\Big(64_{T_1}\mathrm{M}^2_J\mathrm{k}^2_{\xi_{T_1}}\mathrm{k}^2_{\xi_{T_1}}\Big)\mathrm{e}^{8_{T_1}\mathrm{M}_J\mathrm{k}_{\xi_{T_1}}\mathrm{k}_{\xi_{T_1}}}(t_1-t_0)\int_{t_0}^{t_1}\mathbb{E}[\|r^1_s\|^2_Y]ds$$

Altogether, we get that

$$
\begin{aligned}
&\mathbb{E}\Big[\Big(\sup_{t_2\in[t_1,T_1]} \mathrm{e}^{\int_{t_1}^{t_2}\|A_1(s)\|ds}\|u^1_{t_1}\|\Big)^2\Big] \le \mathrm{e}^{4\mathrm{k}^2_{\xi_{T_1}}}\,\mathbb{E}[\|u^1_{t_1}\|^2_{B_Y}] + \mathrm{e}^{(8+2M_j)\mathrm{k}^2_{\xi_{T_1}}}\,\mathbb{E}[\|u^1_{t_0}\|^2_Y] \\
&+ \mathrm{e}^{8\mathrm{k}^2_{\xi_{T_1}}+2M_j\mathrm{k}^2_{\xi_{T_1}}}\,T_1^2\mathbb{E}[\|r^1_s\|^2_{B_Y}] + \mathrm{k}_{suf}\sqrt{\pi}\Big(64_{T_1}\mathrm{M}_J^2\mathrm{k}^2_{\xi_{T_1}}\,\mathrm{k}^2_{\xi_{T_1}}\Big)\mathrm{e}^{8_{T_1}\mathrm{M}_J\mathrm{k}^2_{\xi_{T_1}}}\,\mathbb{E}[\|u^1_{t_0}\|^2_Y] \\
&+ \mathrm{k}_{suf}\sqrt{\pi}\Big(64_{T_1}\mathrm{M}_J^2\mathrm{k}^2_{\xi_{T_1}}\,\mathrm{k}^2_{\xi_{T_1}}\Big)\mathrm{e}^{8_{T_1}\mathrm{M}_J\mathrm{k}^2_{\xi_{T_1}}}\,T_1^2\mathbb{E}[\|r^1\|^2_{B_Y}] \\
&\le \mathrm{k}_{suf}\mathrm{e}^{\mathrm{k}_{suf}\mathrm{k}^2_{2,\xi_{T_1}}}\Big(\mathbb{E}[\|u^1_{t_0}\|^2_Y] + \mathbb{E}[\|u^1_{t_1}\|^2_{B_Y}] + \mathbb{E}[\|r^1\|^2_{B_Y}]\Big) \qquad (87)
\end{aligned}
$$

Similar calculations yield the estimate

$$
\begin{aligned}
&\mathbb{E}\Big[\Big(\sup_{t_2\in[t_1,T_1]}\Big|\mathrm{e}^{\int_{t_1}^{t_2}\|A_1(s)\|ds}-1\Big|\|u^1_{t_1}\|\Big)^2\Big] \\
&\qquad\le |t_1-t_2|^2\mathrm{k}_{suf}\mathrm{e}^{\mathrm{k}_{suf}\mathrm{k}^2_{2,\xi_{T_1}}}\Big(\mathbb{E}[\|u_0\|^2_Y] + \mathbb{E}[\|u^1_{t_1}\|^2_{B_Y}] + \mathbb{E}[\|r^1\|^2_{B_Y}]\Big). \qquad (88)
\end{aligned}
$$

■

7.3 Definitions and Theorems

In the following (unless otherwise specified) X will denote a Banach space.

Definition 1 (Sectorial operator, see Def. 1.2.1 in [7]). *A closed linear operator $A: D(A)\subseteq X\to X$ is said to be a* sectorial operator *of type κ, with $\kappa\in(0,\pi)$ if:*

$$
\sigma(A)\subset\overline{\Sigma}_\kappa,\Sigma_\kappa := \Big\{\lambda\in\mathbb{C}\backslash\{0\} : |\arg(\lambda)|<\kappa\Big\},
$$

$$
\|R_\lambda(A)\|_{\mathcal{L}(X)} \le \frac{M}{|\lambda|}, \quad \forall\lambda\notin\overline{\Sigma}_{\kappa'},\kappa'\in(\kappa,\pi).
$$

As usual, $\sigma(A)$ denotes the spectrum and $R_\lambda(A)$ the resolvent of the operator A. The set of sectorial operators on X of the type κ is denoted by $\mathbb{S}_\kappa(X)$. The set of sectorial operators on X is denoted by $\mathbb{S}(X) := \bigcup_{\kappa\in(0,\pi)}\mathbb{S}_\kappa(X)$. The spectral angle κ_A of $A\in\mathbb{S}(X)$ is given by

$$
\kappa_A := \inf\{\kappa\in(0,\pi) : A\in\mathbb{S}_\kappa(X)\}.
$$

Definition 2 (Bessel potential space, see [2]). *The space $H^s_p(\mathbb{R}^n)$ with $s\in\mathbb{R}$ and $1<p<\infty$ is the function space defined by*

$$
H^s_p(\mathbb{R}^n) := \Big\{f\in\mathcal{S}'(\mathbb{R}^n) : \mathfrak{F}^{-1}\big[(1+|\xi|^2)^{\frac{s}{2}}\mathfrak{F}f\big]\in L^p(\mathbb{R}^n)\Big\} \qquad (89)
$$

$$
\|f\|_{H^s_p(\mathbb{R}^n)} := \|\mathfrak{F}^{-1}\big[(1+|\xi|^2)^{\frac{s}{2}}\mathfrak{F}f\big]\|_{L^p(\mathbb{R}^n)}, \qquad (90)
$$

where $\mathcal{S}'(\mathbb{R}^n)$ denotes the dual of the Schwartz space of rapidly decreasing functions

$$
\mathcal{S}(\mathbb{R}^n) := \{u\in C^\infty(\mathbb{R}^n) \;:\; \forall\;\alpha,\;\beta\in\mathbb{N}^n\;\sup_{\mathbf{x}\in R^n}|\mathbf{x}^\alpha D^\beta u(\mathbf{x})|<\infty\}
$$

and $\mathfrak{F}$ is the usual Fourier transform operator.
Alternatively (see [18]), it can also be defined as the space of all distributions in $\mathbb{R}^n$ such that

$$
G_s * g \in L^p(\mathbb{R}^n),
$$

where $G_s := \mathfrak{F}^{-1}[(1+|\xi|^2)^{\frac{s}{2}}]$ denotes the Bessel potential of order s and $*$ the convolution product.

Definition 3. *Let $\mathfrak{D}$ be a bounded Lipschitz domain in $\mathbb{R}^n$. $u\in H^s_p(\mathfrak{D})$ is an equivalence class of functions $U\in H^s_p(\mathbb{R}^n)$ such that $U|_{\mathfrak{D}}=u$. That is a function u is said to be in $H^s_p(\mathfrak{D})$ if and only if there exits a function $U\in H^s_p(\mathbb{R}^n)$ such that $U|_{\mathfrak{D}}=u$.*
Moreover, $H^s_p(\mathfrak{D})$ endowed with the norm

$$
\|u\|_{H^s_p(\mathfrak{D})} := \inf_{\substack{U|_{\mathfrak{D}}=u,\\ U\in H^s_p(\mathbb{R}^n)}}\|U\|_{H^s_p(\mathbb{R}^n)}
$$

is a Banach space.

Remark 3 ([18]).

1. *For* $s \in \mathbb{R}$, $H^s(\mathfrak{D}) = W_2^s(\mathfrak{D})$ *in norm equivalence. Thereby,* $H^s(\mathfrak{D}) := H_2^s(\mathfrak{D})$.
2. *For* $m \in \mathbb{N}$ *and* $1 < p < \infty$, $H_p^m(\mathfrak{D}) = W_p^m(\mathfrak{D})$ *in norm equivalence.*
3. $W_p^s(\mathbb{R}^n) \subseteq H_p^s(\mathbb{R}^n), \quad 1 < p \leq 2.$
4. $H_p^s(\mathbb{R}^n) \subseteq W_p^s(\mathbb{R}^n), \quad 2 \leq p < \infty$. *This implies that: for* $\mathfrak{D} \subset \mathbb{R}^n$ *a bounded Lipschitz domain,* $H_p^s(\mathfrak{D}) \subset W_p^s(\mathfrak{D})$, $2 < p < \infty$. *Indeed, since* $W_p^s(\overline{\mathfrak{D}})$ *is defined in a way analogous to the definition of* $H_p^s(\mathfrak{D})$ *and due to the inclusion* $H^s(\mathbb{R}^n) \subset W_p^s(\mathbb{R}^n)$, $U \in H_p^s(\mathbb{R}^n)$ *with* $U|_{\mathfrak{D}} = u$ *implies* $U \in W_p^s(\mathbb{R}^n)$ *with* $U|_{\mathfrak{D}} = u$. *Moreover,* $\|u\|_{H_p^s(\mathfrak{D})} \geq \|u\|_{W_p^s(\mathfrak{D})}$ *since*
$$\|u\|_{H_p^s(\mathfrak{D})} := \inf_{\substack{U|_{\mathfrak{D}}=u,\\ U\in H_p^s(\mathbb{R}^n)}} \|U\|_{H_p^s(\mathbb{R}^n)} \geq \inf_{\substack{U|_{\mathfrak{D}}=u,\\ U\in W_p^s(\mathbb{R}^n)}} \|U\|_{W_p^s(\mathbb{R}^n)} =: \|u\|_{W_p^s(\overline{\mathfrak{D}})}.$$
The claim follows from the fact that $W_p^s(\mathfrak{D}) = W_p^s(\overline{\mathfrak{D}})$ *for a bounded Lipschitz domain* $\mathfrak{D}$.
5. $H_p^{s_1}(\mathbb{R}^n) \subset W_p^{s_2}(\mathbb{R}^n) \subset H_p^{s_3}(\mathbb{R}^n) \subset W_p^{s_4}(\mathbb{R}^n)$, *for* $s_1 > s_2 > s_3 > s_4$.

   As in item 4. this implies that for a bounded Lipschitz domain
$$H_p^{s_1}(\mathfrak{D}) \subset W_p^{s_2}(\mathfrak{D}) \subset H_p^{s_3}(\mathfrak{D}) \subset W_p^{s_4}(\mathfrak{D}), \quad s_1 > s_2 > s_3 > s_4$$

Definition 4 (Uniformly bounded function space, see Sec. 1.2.1 [53]). *Let* $[a,\, b]$ *be a closed interval of* $\mathbb{R}$ *and* X *a Banach space, then by* $B_X := B([a,\, b]; X)$ *we denote the space of uniformly bounded functions on* $[a, b]$ *(not necessarily smooth or measurable) with values in* X.

The space $\Big(B([a,\, b]; X), \|\cdot\|_{B_X}\Big)$, with $\|f\|_{B_X} := \sup_{a\leq t\leq b} \|f(t)\|_X$ is a Banach space.

Definition 5 (Hölder continuous function space, see Sec. 1.2.3 [53]). *Let* $[a,\, b]$ *be a closed interval of* $\mathbb{R}$ *and* X *a Banach space, then for* $0 < \mu < 1$, $C^{\mu}_{\{a\}}([a,\, b]; X)$ *denotes the space of* X*-valued functions that are continuous on the* $[a, b]$ *and are* μ*-Hölder continuous at least at* a. *It is endowed with the norm*
$$\|f\|_{C^{\mu}_{\{a\}}} := \max_{t\in[a,b]} \|f\|_X + \sup_{t\in[a,b]} \frac{\|f(t) - f(a)\|_X}{(t-a)^{\mu}}$$
The space of continuous functions on $[a, b]$ with values in the Banach space X is denoted by $C_X := C([a, b]; X)$. It is endowed with the usual norm $\|f\|_{C_X} := \max_{t\in[a,b]} \|f(t)\|_X$.

Definition 6 (Weighted Hölder continuous functions, see Sec. 1.2.4 of [53]). *The space* $F^{\eta,\rho}((a,\, b]; X)$ *with* $0 < \rho < \eta \leq 1$ *consists of* $X-$*valued functions on* $(a,\, b]$ *(resp.* $[a,\, b]$*) when* $\eta < 1$ *(resp.* $\eta = 1$*) with the following properties:*

1. When $\eta < 1$, *the function* $(t-a)^{1-\eta} f(t)$ *has a limit for* $t \to a$.

2. f *is a Hölder continuous function with the weight* $(s-a)^{1-\eta+\rho}$ *and with exponent* ρ, *i.e.*
$$\sup_{a\leq s<t\leq b} \frac{(s-a)^{1-\eta+\rho}\|f(t) - f(s)\|_X}{|t-s|^{\rho}} = \sup_{a<t\leq b} \sup_{a\leq s<t} \frac{(s-a)^{1-\eta+\rho}\|f(t) - f(s)\|_X}{|t-s|^{\rho}} < \infty.$$
3. As $t \to a$, *it holds that* $w_f(t) \to 0$, *where*
$$w_f(t) := \sup_{a\leq s<t} \frac{(s-a)^{1-\eta+\rho}\|f(t) - f(s)\|_X}{|t-s|^{\rho}}.$$
4. The space $F^{\eta,\rho}$ *equipped with the norm*
$$\|f\|_{F^{\eta,\rho}} := \sup_{a\leq t\leq b} (t-a)^{1-\eta}\|f(t)\|_X + \sup_{a<t\leq b} \sup_{a\leq s<t} \frac{(s-a)^{1-\eta+\rho}\|f(t) - f(s)\|_X}{|t-s|^{\rho}}$$
is a Banach space.

Remark 4. *1. If* $0 < \rho' < \rho < \eta \leq 1$, *then* $F^{\eta,\rho} \subset F^{\eta,\rho'}$.

2. If $\eta' < \eta$, *then* $F^{\eta,\rho} \subset F^{\eta',\rho}$, *with* $0 < \rho < \eta' < \eta$.

3. Let $g \in C^{\rho}([0, b]; X)$, *with* $g(0) = 0$, *then for* $0 < \rho < \eta < 1$ *the function* $f(t) := t^{\eta-1}g(t)$ *belongs to* $F^{\eta,\rho}((0, b]; X)$.

Theorem 7.5 (Theorem 3.9 and Theorem 3.10, [53]). *Consider the Cauchy problem*

$$\left.\begin{array}{l}\frac{d}{dt}u + A(t)u = f(t) \quad \text{in } X, \quad t \in (0,T] \\ u(0) = u_0\end{array}\right\} \tag{91}$$

Let $A(t)$ be a sectorial operator with a uniform spectral angle $\kappa < \frac{\pi}{2}$ and a uniform resolvent estimate

$$\|R_\lambda(A(t))\| \leq \frac{M}{|\lambda|}, \quad \kappa \notin \overline{\Sigma}_\kappa, \ t \in [0,T].$$

Moreover, the domain of $A(t)$ may vary in time, but must satisfy the following conditions:

$$\left.\begin{array}{l}D(A(t)) \subset D(A^\nu(s)), \ s,t \in [0,T], \quad \nu \in (0,1] \\ \|A^\nu(t)(A^{-1}(t) - A^{-1}(s))\| \leq C|t-s|^\mu, \quad \mu \in (0,1] \\ 1 < \mu + \nu\end{array}\right\} \tag{92}$$

Also, let $f \in F^{\beta,\sigma}((0,T];X)$, with $\sigma < \min(\beta, \mu+\nu-1)$.
Then for every $u_0 \in D(A(0)^\beta)$ there exists a unique solution u of (91) given by

$$u(t) = U(t,0)u_0 + \int_0^t U(t,s)f(s), \quad t \in [0,T],$$

*where $U(t,s)$ denotes the evolution operator as per Theorem 3.8 [**?**, YAGI09] Also, u satisfies the following estimates:*

$$u \in C([0,T];X) \cap C^1((0,T];X), \quad A(t)^\beta u \in C([0,T];X), \quad A(t)u \in F^{\beta,\sigma}((0,T];X),$$

with

$$\|u(t)\|_{B_X} + \|A(t)^\beta u\|_{C_X} \leq \mathrm{k}(\|A(0)^\beta u_0\|_X + \|f\|_{F^{\beta,\sigma}}).$$

$$\|\frac{d}{dt}u(t)\|_{F^{\beta,\sigma}} + \|A(t)u\|_{F^{\beta,\sigma}} \leq \mathrm{k}(\|A(0)^\beta u_0\|_X + \|f\|_{F^{\beta,\sigma}}),$$

where k denotes some positive constant.

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